2.6 Endocrine disruptors and neurodevelopment in children and wildlife

2.6.1 Overview of neurodevelopmental problems in humans and wildlife and evidence for endocrine disruption

There is currently considerable concern about a potential relationship between increasing prevalence of neurodevelopmental disorders and the increase in exposure to pollutants over the past several decades (Landrigan & Goldman, 2011a; 2011b; Weiss & Landrigan, 2000). Since the 1970s, there have been dramatic increases in previously rare neurodevelopmental disorders. For example, in the 1970s autism prevalence was estimated to be between 4 and 5 in 10,000 children (Wing et al., 1976) but today this value is estimated to be 1 in 110 children (Rice, 2007). Similar trends have been observed for other neurobehavioural problems such as ADHD (attention deficit hyperactivity disorder) and autistic disorder (**Figures 2.12** and **2.13**), learning disabilities and childhood and adult depressive disorders. Predominant among these disorders are attention deficit disorders (ADD) – with or without hyperactivity – with a worldwide pooled prevalence estimate of about 5.3% (Polanczyk et al., 2007). Whilst the increase in autism spectrum disorders is indisputable, questions remain as to whether the increase in the incidence and prevalence of ADHD represent a true increase rather than an artefact due to more agressive disagnosis and reporting.

There are also questions regarding whether there are biological determinants of ADHD that may be impacted by the environment. There are brain imaging studies that support the concept that there are biological differences between children with ADD compared to those children without ADD (Aguiar, Eubig & Schantz, 2010). In addition, genetic studies show a link between ADHD and genotype, though this is modified by environment (Khan & Faraone, 2006). Therefore, it remains a significant challenge to identify the possible causes of the increased incidence – either geographical or temporal – and to determine the extent to which environmental factors play a role (Aguiar, Eubig & Schantz, 2010).

The observation of Paracelsus that women with goitre gave birth to children with severe mental retardation was an early indication that environmental factors could affect brain development and neurobehaviour (Cranefield & Federn, 1963). Likewise, lead poisoning has been known to cause neurotoxicity for millennia, though this was believed to be a disease of adults working in occupations in which lead exposure was very high (Needleman, 2009). Since then, our knowledge of the relationship between neurodevelopmental disorders and chemical exposure has advanced. It is now clear that children – especially during fetal development – are sensitive to the neurotoxic effects of lead and mercury, and at low levels (e.g. Needleman, 2009). It is less widely appreciated that hormones play many critical roles in neurodevelopment and, therefore, associations between chemical exposures and neurobehavioral disorders in humans and wildlife could be plausibly related to disruptions of endocrine pathways. Perturbations in thyroid hormone homeostasis during early life can alter the neuroendocrine circuits that co-ordinate sex-

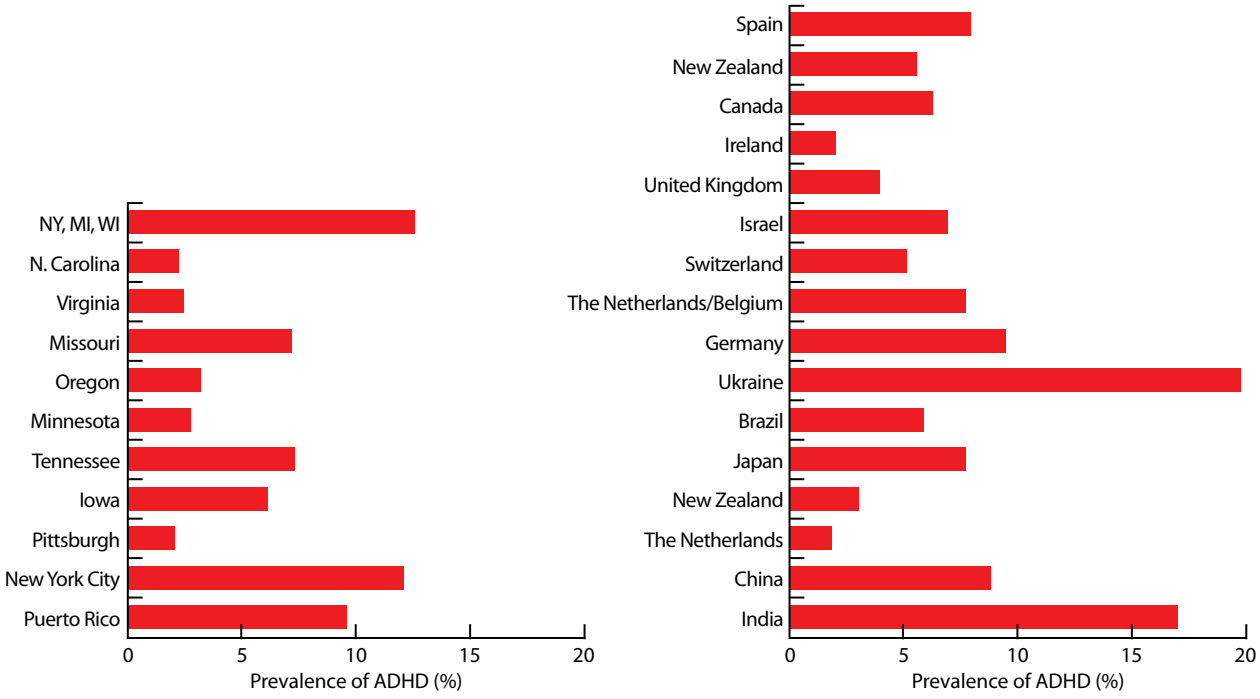

Figure 2.12. Worldwide prevalence of ADHD in children (http://www.medscape.org/viewarticle/547415). Figure reproduced with publisher's permission.

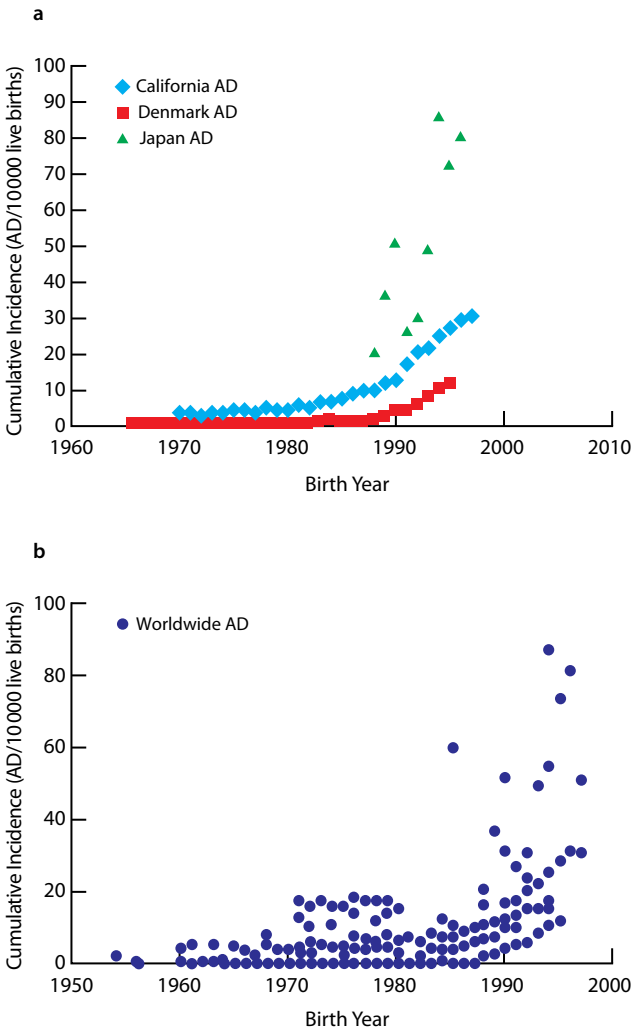

Figure 2.13. Autistic disorder (AD) cumulative incidence time series by cohort birth year from the literature for (a) Denmark, California, and Kohoku Ward, Japan and (b) worldwide AD cumulative incidence. Figure taken from: Timing of Increased Autistic Disorder Cumulative Incidence. (Figure from McDonald & Paul (2010), redrawn; Used with publisher's permission)

specific physiology and behaviour (Jugan, Levi & Bloneau, 2010) and lead to a series of psychiatric and behavioural conditions that are becoming increasingly evident in our society (Gore, 2008, Mclachlan, 2001). The reproductive hormones – estrogens, androgens, progestins – likewise have important effects on neurodevelopment and childhood behaviour, as well as effects on the brain of adults and adult disease. Receptors of these hormones are expressed in the developing brain – in some cases under regulation by other hormones - indicating the great number of interactions hormone systems have on the developing brain. Not only are these hormones involved in the development of sex-typical behaviours – critical attributes in wildlife populations – but they are also involved in the development of other brain structures.

Evidence suggests that endocrine disrupting chemicals can interfere with neurodevelopment affecting cognition and sexual behaviour in both wildlife and humans:

- **There are sufficient data in human populations to conclude that exposures to PCBs during fetal development are linked to general cognitive deficits (e.g., lower global intelligence quotient).** Even in studies of relatively low exposures, PCBs are correlated with measures of cognitive function.
- **Alterations in sexually dimorphic behaviours are seen in human populations highly exposed to PCBs.**
- **Limited data exist to show that *in utero* exposure to other EDCs also affects cognition and sexually dimorphic behaviours in animal studies.**
- **Recent studies of aquatic birds and fish suggest that methylmercury exposure at environmentally relevant levels can interfere with reproductive success** due either to overt neurotoxicity or more subtle neuroendocrine disruptive effects. Methylmercury-exposed birds in the field and in the laboratory have shown altered testosterone and estradiol concentrations (Frederick & Jayasena, 2011), as well as altered courtship behaviour, altered song (Hallinger et al., 2010), high levels of male-male pairing and reduced reproductive success (Frederick & Jayasena, 2011). Reproductive behaviours are also affected in fish exposed to environmentally relevant concentrations of methylmercury (Hammerschmidt et al., 2002; Sandheinrich & Miller, 2006), likely due to its effects on the endocrine system (Crump & Trudeau, 2009).
- **Many areas of the world are still inhabited by wild mammals with levels of methyl-mercury in their tissues that would be unsafe for rodents and humans** (Basu & Head, 2010; Mergler et al., 2007).

2.6.1.1 Thyroid hormone insufficiency and brain development

The neurobehavioural impacts of thyroid hormone insufficiency in humans are so clear that there is universal screening of thyroid function in all regions of the world (LaFranchi, 2010). To understand the ways in which exposure to endocrine disruptors could affect brain development, it is necessary to understand the complexities of the development of both the neurologic and thyroid systems and how thyroid hormones regulate brain development.

Figure 2.14 illustrates the three stages of neurological development in relation to thyroid hormone during fetal development, thus highlighting why the fetus is sensitive to thyroid hormone disruption (Williams, 2008). There are three stages of thyroid hormone-dependent neurological development depicted in the figure: the first is before the onset of fetal thyroid hormone synthesis (16-20 weeks post conception in humans), the second is during the rest of pregnancy, when the developing brain derives thyroid hormones from both the mother and the fetus, and the third is in the neonatal and post-natal period when thyroid hormone supplies are derived from the child. Thyroid hormone plays

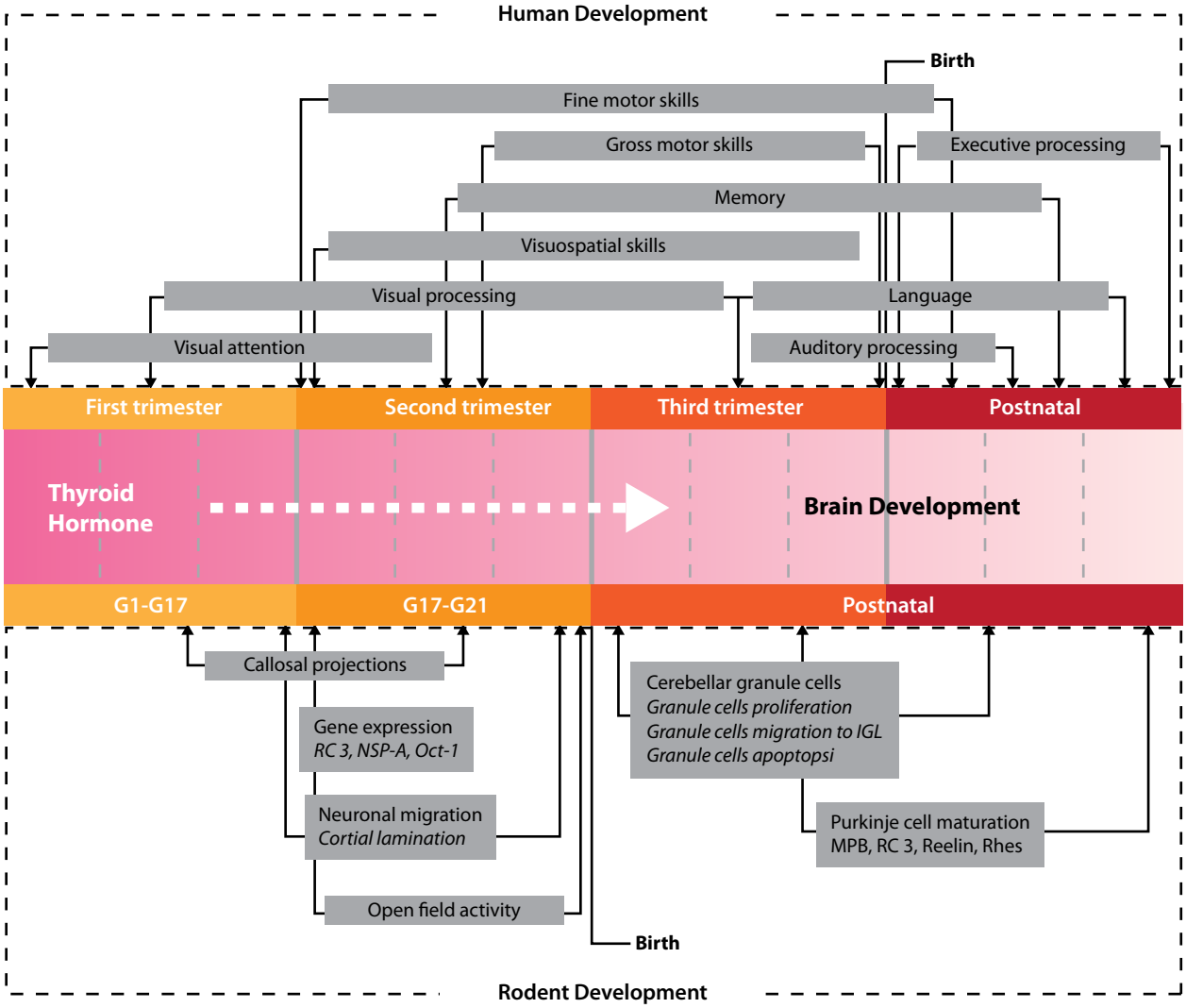

Figure 2.14. Relationship between thyroid hormone action and development of the brain. In the first trimester of pregnancy, early neuronal proliferation and migration is dependent on maternal thyroxine (T4). By the end of the first trimester, development of the hypothalamic-pituitary axis has occurred and a surge in thyroid-stimulating hormone (TSH) secretion results in the onset of fetal thyroid hormone production and increasing occupation of thyroid hormone receptors (TRs) by T3. Continuing development of the brain in the second and third trimesters relies increasingly on T4 produced by both the fetus and mother. Continued post-natal development is entirely dependent on neonatal thyroid hormone production (Figure based on Zoeller & Rovet, 2004).

different roles in different parts of the brain at various times during development (Zoeller & Rovet, 2004). It is delivered to the brain in a complex shuttling system. Largely, T_4 is transported across the blood brain barrier by specific transporters, converted to T_3 in the supporting (glial) cells, and then further transported to neurons (Bernal, 2005). Thus, it is a combination of transporters and enzymes that regulate the delivery of the hormonally active T_3 to its targets. These targets are both glial cells and neurons. For example, the cells that produce the insulating sheath (myelin) around the axons in the brain are dependent upon thyroid hormone (Billon et al., 2002) and animals with low thyroid hormone show progressively fewer of these cells in the major bridge between the two hemispheres of the brain (Sharlin et al., 2008). Genetic defects of the T_3 transporter in humans cause several mental deficits to occur (Maranduba et al., 2006; Schwartz et al., 2005; Visser et al., 2009).

2.6.1.2 The role of hormones in brain development

Sex steroids

In addition to the changes in thyroid hormone exposure during early development, both male and female rodent embryos are exposed to a changing milieu of sex steroid hormones during the late embryonic and early postnatal period that cause permanent sexually dimorphic differences in the size, cell number and neurochemistry of hypothalamic regions of the brain (reviewed in McCarthy, 2009). Because male and female embryos are exposed to different genetic and hormonal environments, the brains of male and female newborns are substantially different from the day of birth. The existence of a genetic contribution to the control of sexual dimorphisms in neurobiology and sexual orientation is firmly established, although the specific genes implicated in the process are not known. The role of hormones in human sexual

orientation is less well understood. Balthazart (2011) reviews the literature indicating that sex steroid hormones may act in concert with genetic factors as well as features of the social postnatal environment to influence sexual orientation.

Balthazart (2011) reviews the literature indicating that sex steroid hormones may act in concert with genetic factors - and features of the postnatal social environment - to influence sexual orientation in humans. This review emphasizes the heuristic value of studies of girls with a medical condition known as congenital adrenal hyperplasia (CAH). These girls are exposed in utero to high levels of androgens from the adrenal glands and exhibit, as a population, masculinization of various behaviors including aggressive play and increased probability of homosexual relationships (30-40 % in some studies compared to 10% in case controls or unaffected sisters) (Balthazart, 2011).

Other morphological and physiological characteristics also appear to be influenced by prenatal testosterone in CAH women, such as the ratio of the lengths of the second to fourth fingers which differs between males and females (Hampson, Ellis & Tenk, 2008) and is clearly masculinized in these women (Breedlove, 2010).

In rodent models of human physiology, studies show that sex differences in brain structure are caused by differences in hormone action early in fetal development. These structural differences are irreversible and are parallel to the effects of hormones early in development on adult sex behavior. Thus, hormones act early in development to organize the nervous system in such a way that hormones in the adult can activate sex-typical behaviours. In rodents, exposure to the male hormone testosterone induces the preference for a feminine sexual partner. Thus, genetic males or genetic females exposed to testosterone will orient toward a female. In contrast, the absence of testosterone leads to preference for a masculine partner; genetic males or females deprived of testosterone during development will orient toward a normal male. It is also important to recognize that testosterone is converted to estrogen in the male brain, and it is estrogen that is responsible for sexual orientation (Henley, Nunez & Clemens, 2009; 2011).

Hypothalamic and pituitary hormones

Multiple hypothalamic neuropeptides and neurotransmitters as well as pituitary hormones exert control over sexual behaviour and reproduction in vertebrate animals including humans (reviewed in Dickerson & Gore, 2007). The reproductive neuroendocrine axis in vertebrates is regulated by the gonadotropin releasing hormone (GnRH) neurosecretory system, located at the base of the hypothalamus. In the pituitary, GnRH binds to its receptors and stimulates the synthesis and release of the gonadotrophic hormones LH and FSH into the general circulation. The gonadotrophins act at the gonads (ovaries and testes) to stimulate sex steroid production, gonadal maturation and sperm and egg production. These three levels of the hypothalamic, pituitary gonadal axis function both independently and interdependently and thus a dysfunction at one level has consequences for the other levels. Moreover, neurotransmitters also modulate the release of GnRH.

Each neurotransmitter may have more than one type of receptor on more than one type of cell and therefore, alterations in the level of a single neurotransmitter may affect multiple cells in different ways. Chemical contaminants can affect both neurotransmission and neurosecretion via various mechanisms. Minor changes in neuronal function may cause major changes in sexual behaviour.

2.6.2 Evidence for endocrine disruption of neurodevelopment in children and in rodent models

2.6.2.1 Attention deficit disorders

There are a number of studies that support the hypothesis that specific environmental factors represent risk factors for ADD. Lead and PCB exposures represent important cases of environmental contaminants associated with ADD in children (Eubig, Aguiar & Schantz, 2010). Exposure to lead is particularly high in developing countries like in many parts of Africa where more than one third of the children still suffer high levels of lead exposure (Falk, 2003). In developed countries, on the other hand, only a small minority of children (mainly the urban poor) are still affected by high levels of lead (reviewed in WHO, 2003). Likewise, attention deficit is over represented in children whose mothers exhibited low thyroid hormone in the first trimester of pregnancy (Haddow et al., 1999) or in children with prenatal ethanol exposure (Mattson, Crocker & Nguyen, 2011). Finally ADD has been linked to elevated exposure to a variety of organophosphate pesticides (Bouchard et al., 2010; Kuehn 2010; Marks et al., 2010; Riccio, Avila & Ash, 2010; Schettler 2001; Xu et al., 2011) still found in relatively large segments of human populations (see Chapter 3.1.1.6 & 3.2.2.2). Thus, overall, although there is uncertainty about causes of the increased incidence and prevalence of ADD in children worldwide, there is plausible evidence to conclude that some environmental chemicals are associated with this disorder.

2.6.2.2 General cognitive deficits and PCB exposure

A very large number of studies have been published over the past 10 years designed to characterize exposures of children to industrial chemicals and to test whether they are related to measures of cognitive deficits in children. In particular, the relationship between exposures to PCBs and measures of cognitive function has been well-studied. Despite the fact that PCB production was banned in the late 1970s, they are still found in all environments and all human and animal tissues (see Chapter 3 for a comprehensive review). The relationship between PCB exposure and cognitive function is an important topic (reviewed by Carpenter, 2006) for the following reasons: 1) a large number of high quality studies have been published on human populations around the world, 2) exposure assessment has become quite sophisticated, and 3) cell-free,

cell-based, and animal studies provide important insights into the mechanisms by which these and other endocrine disrupting chemicals can produce neurotoxic effects.

There are sufficient data in human populations to conclude that exposures to PCBs during fetal development are linked to general cognitive deficits (e.g., lower global intelligence quotient). In highly exposed populations, the most consistent effects across all studies were impaired executive functioning, followed by processing speed, verbal ability and visual recognition memory. These populations include: the Yu-Cheng children in Taiwan (born to mothers exposed to thermally degraded PCBs between 1978 and 1979; Chen et al., 1992), the Dutch cohort (Patandin et al., 1999), the Lake Michigan cohort of children born to mothers who ate PCB contaminated fish (Jacobson & Jacobson 1996; 2003), the Dusseldorf cohort (Walkowiak et al., 2001; Winneke et al., 1998) and the Slovakian cohort (Park et al., 2009). Moreover, even in studies of relatively low exposures, PCBs are correlated with measures of cognitive function, including impulse control (Stewart et al., 1999; 2000; 2003a; 2003b; 2005; 2000; 2008; 2006).

In addition to the cognitive deficits observed, the Yu-Cheng children also exhibited alterations in sexually dimorphic behaviour with exposed boys having a deficit in spatial abilities (Guo et al., 2004). Exposure to higher ambient levels of PCBs has also been associated with less masculinized play in boys and more masculinized play in girls in a group of Dutch school children (Vreugdenhil et al., 2004).

PCB levels detected in blood today are markedly lower than they were in the 1970s – 1990s and a study carried out in Germany recently suggested that exposure to PCBs at current exposure levels does not impair neurodevelopment. This conclusion was based on studying two populations in close proximity to each other in Germany (Wilhelm et al., 2008). Taken together, the available epidemiological evidence is sufficient to conclude that PCB exposures during fetal development are linked to measures of cognitive deficits (Schantz, Widholm & Rice, 2003).

2.6.2.3 Animal studies with PCBs

The mechanism(s) by which PCBs produce developmental neurotoxic effects have been studied extensively. A dominant theory is that PCBs can interfere with thyroid hormone signalling during development. Many of the cognitive deficits linked to PCB exposures are similar to those associated with pre- and post-natal thyroid hormone insufficiency (Zoeller and Rovet, 2004). Rodent studies almost uniformly show that PCB exposures decrease serum thyroid hormone levels (Bastomsky 1974; Goldey et al., 1995; Zoeller, Dowling & Vas, 2000) and produce effects on brain development that are similar to those seen in PCB-exposed human populations (Goldey & Crofton, 1998; Goldey et al., 1995; Herr, Goldey & Crofton, 1996). Cell-based studies show that some PCB congeners can interfere directly with the thyroid hormone receptor (Gauger et al., 2007; Iwasaki et al., 2002; Koibuchi & Iwasaki, 2006; Miyazaki et al., 2004; Miyazaki et al., 2008).

Even in rodent animal models of humans, however, it is difficult to say with certainty that behavioural or developmental effects of PCB exposure are caused directly by effects on thyroid hormone signalling. Specific PCB congeners can affect the intracellular regulation of calcium in rodent brain that is very important in nerve cell development and function (Pessah, Cherednichenko & Lein, 2010). They can also influence neurogenesis, neuron proliferation and differentiation (Fox et al., 2010), and the dopaminergic system, in vitro and in vivo (Barkley 1998; Kirley et al., 2002; DiMaio, Grizenko & Joober, 2003), thought to be crucial for the pathogenesis of ADHD. Very low doses of PCBs can impact sex steroid-related endpoints in the rodent brain (Dickerson et al., 2011a; Dickerson, Cunningham & Gore, 2011). Therefore, it is not possible to directly demonstrate in animals that PCBs produce neurotoxic effects by acting on thyroid hormone signalling alone or whether in combination with other mechanisms.

Considering this, it is even more difficult to prove that thyroid disruption mediates the effect of PCB exposure on developmental neurotoxicity in humans. A number of studies have evaluated the relationship between serum thyroid hormone and PCB body burden in humans (Miller et al., 2009; Longnecker, 2000). These are challenging studies to review both because the technology associated with PCB measurement has changed over the years, and because there are different measures of thyroid function that have been employed in these studies – as well as differences in the timing of sample collection relative to periods of exposure. In addition, different PCB congeners have different potencies for reducing thyroid hormone levels in rodents (e.g. Giera et al., 2011), and this needs to be considered also in epidemiological studies (Chevrier et al., 2007).

There are several important lessons from the PCB story:

- The only clinical measure of thyroid disruption currently available in humans is serum hormone levels, and therefore it is not currently possible to demonstrate that an association between chemical exposure and hormone level mediates specific adverse effects.
- Thyroid hormone insufficiency produces different effects on cognitive development when it occurs at different times during development (Zoeller & Rovet, 2004). Therefore, the timing of measurements of thyroid function and chemical exposure and the cognitive domains that may be affected by these exposures are critical.
- If chemicals can interfere with thyroid hormone action in a manner that is not revealed by changes in thyroid hormone levels, (as has been shown in animal studies, e.g. Giera et al., 2011), then we currently have no way of testing for this in human studies. Therefore, biomarkers of thyroid hormone action should be developed both for use in the clinic and epidemiological studies.
- No guideline study validated for use in screening or testing evaluates measures of thyroid hormone action; therefore, these chemicals would be missed by regulatory tests designed to screen chemical safety.

2.6.2.4 PBDEs and cognitive disorders

Knowledge of developmental toxicity of PBDEs is limited, although human in vitro and epidemiological studies indicate that they work through the same mechanisms as PCBs to induce effects on neurodevelopment via thyroid hormone disruption (Schreiber et al., 2010; Chevrier et al., 2010). Johnson-Restrepo & Kannan (2009) determined that infant daily exposure dose of PBDEs in the USA due to inhalation, incidental oral ingestion and dermal absorption of house dust were significantly higher than in adults. Moreover, serum samples of infants aged 0-4 years contained significantly higher PBDE concentrations as compared to children of 5-15 years of age in an Australian population (Toms et al., 2008). The major exposure route to PBDEs, however, is through maternal exposure in breast milk (reviewed in Chapter 3.2).

There are few epidemiological studies on the neurodevelopmental effects of PBDEs. A single study of 329 mothers in lower Manhattan, New York, examined 210 cord blood samples for PBDEs and neurodevelopmental effects in the children at 12-48 and 72 months of age. The findings indicated associations between high concentrations of BDE-47, -99 and -100 and lower psychomotor and mental development and IQ (Herbstman et al., 2010). An earlier study (Roze et al., 2009) also reported a similar association.

2.6.2.5 Animal studies with PBDEs

In vivo experimental studies show that maternal exposure of rodent models to individual PBDE congeners or commercial pentabrominated mixtures causes dramatic changes in thyroid hormone levels (Darnerud et al., 2007; Kodavanti et al., 2010) as well as subtle changes in neurobehaviour and both male and female reproductive endpoints (Kodavanti et al., 2010). Various studies also report long lasting hyperactivity and reduced performance in learning and memory tests (e.g. Branchi et al., 2003; 2005; Viberg 2009a; 2009b; Viberg, Fredriksson & Eriksson, 2003; 2004; Viberg, Mundy & Eriksson, 2008; Kuriyama et al., 2007; Hallgren & Darnerud, 2002; Zhou et al., 2002) in a similar fashion to that described for PCBs. Moreover, feminization of sex-steroid dependent behaviour, such as of the sexually dimorphic sweet preference of male rats, was observed following prenatal exposure to BDE-99 (Lilienethal et al., 2006) and to a PCB mixture resembling that found in human breast milk. In both of these cases, the effects on behaviour appeared to coincide with decreasing aromatase activity in the hypothalamic/pre-optic area of the brain, inhibiting the local production of the hormone estradiol (one of the main processes by which the brain becomes male-like). Parallel to these behavioural changes, alterations in proteins involved in neuronal survival, growth and synaptogenesis are seen (Dingemans, Van den Berg & Westerink, 2011). It is important to note that behavioural toxicity in rodents can also occur without alternations in maternal serum T4 (Gee & Moser, 2008; Gee, Hedge & Moser, 2008).

2.6.2.6 Mercury and neurodevelopment

Metals such as lead and mercury can also impair neurodevelopment through direct neurotoxic effects, through effects on thyroid function or through epigenetic mechanisms (Ellingsen et al., 2000; Takser et al., 2005). Methylmercury induced disruption of GABAergic signalling in the brain under probable and relevant exposure scenarios can have profound consequences as GABA (A) is the main inhibitory neurotransmitter in the mammalian brain, accounting for 50% of synapses in certain brain regions. Exposure to methylmercury results in build-up of GABA (A) neurotransmitter levels in the synapse and a corresponding decrease in GABA (A) receptor levels (Basu et al., 2010). It also reduces the availability of selenium which is essential for deiodinase activity that in turn activates and inactivates thyroid hormone in the brain and other tissues.

There is a particular current concern about methylmercury because of its high levels in the diet (Trasande et al., 2006; see Chapter 3.1.3). Historical incidences of methylmercury poisoning led to neurodevelopmental impairments in prenatally exposed children.

Consumption of fish is the primary route via which humans are exposed to methylmercury and it is estimated that 8-16% of USA newborns have cord blood levels higher than acceptable limits (Trasande, Landrigan & Schechter, 2005), although this percentage is higher in populations in all parts of the world that rely more heavily on fish for sustenance (Hightower, O'Hare & Hernandez, 2006), particularly in developing countries where fish-eating communities may be exposed to pollution from mercury processing plants (Oosthuizen & Ehrlich, 2001).

In West Greenland, for example, the levels of mercury in the human diet exceed acceptable tolerable daily levels by 50%, much of which comes from consumption of seal tissues (Johansen et al., 2004). The median concentration in the human brain of 17 Greenlanders was 0.17 µg/g wet weight, although levels of 4mg/g were found in some humans (Pedersen et al., 1999). Furthermore, a study of 43 Inuit children reported that mercury exposure might be related to neurological deficits (Weihe et al., 2002).

In Africa, Nweke & Sanders (2009) report that an important source of direct mercury exposure is the artisanal gold mining and processing when exposure to vaporized elemental mercury occurs during burning to separate the gold-mercury amalgam (Savornin, Niang & Diouf, 2007). Workers typically not equipped with personal protective equipment are at risk as well as children under their care (Van Straaten, 2000). In some countries, the mining and sale of gold are a female-only activity and this may include a workforce between 500 and >100,000 women and children (Hentschel, Hruschka & Priester, 2003).

2.6.2.7 Bisphenol A and phthalates may affect sex-specific behaviours and sex dimorphism in neural development

Yolton et al. (2011) recently showed that the concentrations of BPA and phthalates in maternal urine during early pregnancy

were associated with higher hyperactivity and aggression in 2 yr old girls, but not in boys, consistent with rodent data, suggesting an effect of BPA on sexual dimorphism of these types of behaviour, (Kubo et al., 2003, Rubin et al., 2006). In a further study, juvenile female rats exposed to BPA during gestation and lactation exhibited defeminization of social interactions, including reduced play with males, decreased social grooming, increased play with females and increased sociosexual exploration (Farabollinii, 2002, Porrini et al., 2005). Males exhibited increased aggression at sexual maturation (Kawai et al., 2003) and increased anxiety-related behaviour.

The effects of BPA on the brain and behaviour are assumed to be attributed to its estrogen receptor (ER)-mediated action, but it is not clear how its low potency could account for the strong effects that are observed in many tissues after exposure to relatively low doses. There is also evidence that changes in gene expression in utero persist into adulthood (e.g. Smith & Taylor, 2007; also reviewed by WHO, 2011) and hence possibly involve epigenetic mechanisms (see Chapter 1.3.6). This is supported by evidence that estrogen and some endocrine disruptors have been reported to dynamically change the methylation status of their target genes and that this is of critical importance for the function of the central nervous system; epigenetic mechanisms play a crucial role in neuronal plasticity (Borrelli et al., 2008) and thus are potential targets for neurodevelopmental effects of chemicals that induce cognitive dysfunction in human populations, mainly when the exposure takes place during prenatal and early postnatal development (Vahter, 2008; Bellinger, 2008). Given the widespread use and human exposure to chemicals such as phthalates and BPA (reviewed in Chapter 3.2), this is an important area for further study.

2.6.2.8 Are mixtures of different neuroendocrine disruptors a concern for human health?

There is almost no information concerning the effects of mixtures of neuroendocrine disruptors, even though there is little doubt that PBDEs, PCBs, mercury and several pesticides will co-occur in human tissues. Examples of situations where interactive effects of mixtures been suggested to occur include the combination of methylmercury and PCBs in two large cohorts of children in the Faroe islands (Grandjean et al., 2001; 2004; Roegge et al., 2004). These suggestions are supported by a very limited number of rodent studies in which synergistic changes in neurochemical measures (e.g. Bemis & Seegal, 1999) and increases in neurotoxic effects (Eriksson et al., 2003) have been reported as a result of combined exposures to PCBs and methylmercury.

2.6.3 Evidence for endocrine disruption of neurodevelopment in wildlife

In comparison with the evidence of neurodevelopmental diseases and disorders in humans, data describing patterns of neuroendocrine dysfunction in wildlife are less prevalent, despite the fact that studies on wildlife (particularly mammalian wildlife) can provide important information on environmental exposures, early and sub-clinical effects and clinical neurotoxicity of chemicals in the environment. There is, however, a wealth of literature on the neurotoxicology of mercury, the pesticide DDT, PCBs and PBDEs. Some case studies are highlighted here that add weight to the evidence presented in the human health section of this review on the environmental contaminants of neurotoxic concern to humans.

2.6.3.1 Mammals

Methylmercury, PCBs and PBDEs biomagnify (concentrate) up through aquatic food webs, resulting in high concentrations in fish and other top predators (Chapter 3.1.3 & 3.2). As such, consumption of contaminated fish represents the primary route via which wildlife and humans are exposed to these chemicals.

Methylmercury

Much of our knowledge concerning neurotoxicology of methylmercury was obtained following the human poisoning event in Minimata Bay, Japan, alerted 5 years earlier by the frenzied behaviour of cats, rats, crows and fish (Aronson, 2005). Around this time, population declines in other wildlife species were particularly noticeable in regions that used organomercurial fungicides, or that were located downstream of pulp and paper mills using mercury.

The structural brain lesions and effects of methylmercury are similar across mammals (reviewed in Basu & Head, 2010).The organic form of mercury, methylmercury, crosses the blood-brain barrier and can cause a range of effects on brain tissues in vertebrate wildlife. Lower exposures reduce the levels of key enzymes (cholinesterase and monoamine oxidase) in wild otters (Basu et al., 2007a) and *N*-methyl-D-aspartate (NMDA) glutamate receptors in wild mink (Basu et al., 2007a; 2007b), bald eagles (Rutkiewicz et al., 2011) and polar bears (Basu et al., 2009). These effects have been corroborated in laboratory studies of mammals and fish exposed to methylmercury (Basu et al., 2006; 2007c; 2010; Coccini et al., 2006; Berntssen, Aatland & Handy, 2003) and are of both ecological and physiological concern because these enzymes and receptors are parts of critical neurochemical pathways that control reproduction, cognition, growth and development (Manzo et al., 2001). At the present time, overt episodes of mercury poisoning are rare but there is evidence that lower levels of exposure can affect growth, reproduction and development in wildlife. These effects are much more common in longer-lived species that are higher up in the food web because of the biomagnification of methylmercury through aquatic systems (see Chapter 3.1.3). It is entirely possible that even subtle neurological damage in fish-eating wildlife may be having more severe consequences than we can currently ascertain.

Mammalian wildlife species also accumulate mercury in their brains where it can have subtle effects on the brain neurochemistry (Manzo et al., 2001; Scheuhammer et al.,

2007). Many areas of the world are still inhabited by wild mammals with levels of methylmercury in their tissues that would be unsafe for rodents and humans (Basu & Head, 2010; Mergler et al., 2007). However, it is important to note that there are differences in susceptibility between different species of mammals. For example, levels of mercury in the livers of polar bears in the Canadian Arctic exceeded those in the livers of humans that succumbed to Minimata disease, but there is little observational or experimental evidence of neurological damage in the brains of these bears (Sonne et al., 2007), probably because the levels in the brain stem were markedly lower than in the other tissues of the body (Basu et al., 2009). Notwithstanding this, mercury associated changes in brain NDMA receptor levels were found in these bears, one of the earliest known responses to mercury exposure. In addition, a subsequent study reported an inverse association between mercury exposure and DNA methylation in the lower brain stem of male (but not female) polar bears, suggesting possible long term consequences of mercury exposure for chromosomal stability, disease progression and reproductive function (Pilsner et al., 2010). These results may be of relevance to human health in Greenland as an epidemiological study of 43 Inuit children in Greenland reported that mercury exposure in humans might be related to neurological deficits (Weihe et al., 2002).

PCBs

Most PCBs, particularly those with non-coplanar structures, have intrinsic neurotoxic properties (Mariussen & Fonnum, 2006), and can impede several neurological processes including dopaminergic signalling and calcium homeostasis. Whilst their action on the neurological system is clear, data regarding their accumulation in the brain are sparse. Where these data exist, liver to brain ratios range between 3-fold to more than 7-fold across mammals alone, making it difficult to derive exposure-response relationships (Giesy & Kannan, 1998; Kodavanti et al., 1998). As with mercury, the initial discoveries concerning neurotoxicological effects of PCBs were seen in wildlife. Several PCB mixtures and individual congeners at environmentally relevant levels (e.g. <1µg/g in the diet) could impair numerous health aspects including neuroendocrine function (reviewed in Basu et al., 2007b). PCB bans and restrictions have led to a decline in PCB concentrations in humans and wildlife over the past few decades, although geographic hotspots still exist where certain PCB congeners persist (Chapter 3.2.1 & 3.2.2). A few biomonitoring studies report PCBs in the brain tissues of mammalian wildlife and humans between 2-50 ng/g wet weight. In marine mammals, however, brain PCB levels are higher (up to 450 ng/g wet weight). Dominant congeners in the brain of mammalian wildlife are coplanar and are similar to those found in humans (CB153, 180, 170/190, 138 and 99).

As in humans and rodent models, the most commonly observed effects of PCB exposure is the disruption of thyroid hormone homeostasis. Laboratory studies with mink and with harbour seals have shown PCBs to decrease T3 and T4 (see Chapter 2.5). Moreover in numerous field studies of seals, sea lions and polar bears, decreased serum T4 was correlated with PCB exposure. There is, however, mixed evidence on the impacts of PCBs on brain neurochemistry in mammalian wildlife. In river otters, no significant correlations between brain PCB levels and several neurochemical markers were found (Basu et al., 2007c), whereas in captive female mink and in rodents and monkeys, changes in dopamine levels in the brain and hypothalamus were found following exposure to PCBs (reviewed in Seegal, 1996).

PBDEs

As already mentioned, the levels of PBDEs in the environment rapidly increased with the increasing popularity of PBDEs as flame retardants (Chapter 3.2). In the Baltic Sea, atmospheric deposition of PBDE still exceeds PCBs by a factor of 40X. Between 1981 and 2000, levels of PBDEs in the blubber of Arctic ringed seals and in the marine mammals of the temperate Asia-Pacific region increased about 9-fold (Ikonomou, Rayne & Addison, 2002; Tanabe et al., 2008). A single study reports levels of PBDEs in river otter brain at concentrations ranging from 1.1 to 6.6 ng/g wet weight, comprising only BDEs -99, -100 and -153 (Basu, Scheuhammer & O'Brien, 2007). Levels in avian species in Belgium are reported to be much higher (Voorspoels et al., 2006b): wild sparrows, 140-5800 ng/g; owls, 0.8-174 ng/g; and buzzards 0.2-1600 ng/g. Recent analyses of wildlife and human tissues for PBDEs show some declining concentrations due to restrictions and bans on their use, but levels in wildlife remain highest near urban centres (Voorspoels et al., 2006a) and vary considerably from one country to another as for humans (Chapter 3, sections 3.2.1 & 3.2.2).

There is still much to learn about the neurobehavioral toxicity of PBDEs in mammalian wildlife. In a recent review, Costa & Giordano (2007) concluded that subtle but lasting developmental neuroendocrine effects will occur at levels of PBDEs only marginally higher than currently found in animal tissues. Some of these effects are likely due to anti-thyroidogenic or brain cholinergic mechanisms. There are few if any studies examining this possibility. In a single ecological study on river otters, there were no correlations between cholinesterase activity and PBDE levels in the brain (Basu, Scheuhammer & O'Brien, 2007).

2.6.3.2 Non mammalian vertebrates

Methylmercury

Elevated exposure of fish and amphibians to methylmercury also impairs behaviours that are critical for successful reproduction, avoidance of predators and feeding (e.g. Weis, 2009). Laboratory studies have shown that, in general, the younger animals are more sensitive to the effects; for example, it takes 2-fold higher levels of methylmercury in adult than young fish to negatively affect behaviours (Beckvar, Dillon & Read, 2005). Similarly, in amphibians, maternal exposure negatively affected growth, duration of metamorphic climax, and swimming performance in a study of American toad

larvae. The duration of metamorphic climax is a period of increased vulnerability for immunological, energetic, and ecological reasons, and therefore mercury exposure at this time may increase mortality risk in exposed amphibian populations. It is interesting to note that the metamorphs from mercury-exposed mothers did not have elevated tissue concentrations due to dilution of maternally transferred mercury during growth.

PCBs

Over the last two decades Khan & Thomas (1997; 2001; & 2006) have accumulated substantial evidence on the involvement of PCBs in the disruption of the seratoninergic systems in fish brains. During gonadal recrudescence, PCBs reduce both dopamine and serotonin in various regions of the hypothalamus. This leads to an inhibition of the reproductive luteinizing hormone (LH) and impairment of gonadal growth. As in rats, this fall in dopamine and serotonin is thought to be caused by the inhibition of thyroid hormone induced by PCBs, and highlights the fact that adverse effects of endocrine disruptors on reproduction can also be due to their effects on neurohormones and thus indirectly on gonadal hormones.

PBDEs

In non-mammalian vertebrate wildlife, studies of neurodevelopmental disorders, occurring concomitantly with exposure to PBDEs, can be provided. There are multiple lines of evidence suggesting that PBDEs affect T_4 levels in developmentally exposed birds, fish and amphibians (e.g. Fernie et al., 2006; Lema et al., 2006; 2008; 2009) making it likely that these chemicals also affect neurodevelopment in these animals as in rodent models. The most dramatic effect reported in fish species is a hatching delay (Timme-Laragy, Levin & Di Giulio, 2006), which could be attributed to a T_4 mediated mechanism. Other possible T_4 mediated effects include those on tail curvature direction, hypo activity and elimination of the fright response, with important consequences for predator recognition and avoidance. Increases in thyroid hormone and its receptor occur just before hatching in zebra fish and can be altered by exposure to thyroid hormone receptor antagonists (Liu & Chan 2002).

2.6.4 Neuroendocrine effects of exposure to endocrine disrupting chemicals on courtship behaviour and mate choice in wildlife

2.6.4.1 Methylmercury

Studies of aquatic birds suggest that methyl mercury exposure at environmentally relevant levels can interfere with reproductive success- due either to overt neurotoxicity or more subtle neuroendocrine disruptive effects on courtship behaviour and mate choice. For example, common loons exposed to methylmercury showed increased lethargy, reduced time incubating the nest and foraging and feeding their young (Evers et al., 2008). As a result, adults in areas with higher exposure had decreased hatching success of eggs and production of chicks (Scheuhammer et al., 2007; Evers et al., 2008). High mercury levels in eggs have been suggested as a cause of declining ivory gulls in the Canadian Arctic (Braune, Mallory & Gilchrist, 2006). Moreover, methylmercury-exposed white ibises in the field and in the laboratory have shown altered testosterone and estradiol levels (Frederick & Jayasena, 2011), as well as altered courtship behaviour, altered song (Hallinger et al., 2010), high levels of male-male pairing and reduced reproductive success in successful pairs that did raise young (Frederick & Jayasena, 2011). Male to male pairing has been reported extensively in many animal species but it is most commonly associated with skewed sex ratios or limited mating opportunities. It is notable that this recent study did not report either of these conditions; mating opportunities and sex ratios were approximately equal. Moreover, male to male pairings do not normally occur in wild ibises. The exposure levels encountered in Frederick and Jayasena's study were environmentally relevant and are therefore of relevance to many bird populations. As reproductive output was decreased by both homosexual behaviours and as a result of a reduced number of fledglings raised by heterosexual pairs, mercury exposure could lead to altered demographic patterns in wild bird populations (Burgess & Meyer, 2008; Barr, 1986). Indeed, in the Frederick study, the breeding population size was inversely correlated with their annual methylmercury exposure in South Florida, USA (Frederick & Jayasena, 2011).

2.6.4.2 DDT

DDT is a persistent, widespread environmental contaminant found in most regions of the world and at high concentrations in countries where it is still used to control malaria mosquitoes (Chapter 3.2.1). The most well documented effects of DDT on neurobehaviour are those seen in birds, where DDT has been associated with decreased courtship behaviours (Zala & Penn, 2004), altered singing (in songbirds) and female to female pairing (in gulls). It is well known that administration of testosterone or estradiol to adult female or male birds, respectively, leads to mate attraction and courtship behaviour typical of the opposite sexes. In addition, early developmental exposures to estrogens or aromatase inhibitors has been shown to profoundly increase male and female sexual interest in the same sex and decrease male vigour. Sexual dimorphism of singing is also thought to be controlled not only by sexually dimorphic genes expressed in the brain but also by estrogen (reviewed in Adkins-Reagan, 2011); reducing the concentration of either 17β-estradiol or testosterone reaching the song system in the brain (a set of interconnected brain regions that mediate the learning, perception and vocalization of song) reduces the size of this area, concomitant with decreases in singing activity and song repertoire (Gulledge & Deviche, 1997; Metzdorf, Gahr & Fusani, 1999; Riters et al., 2000, Riters & Teague, 2003;). It is reasonable to hypothesise then that the effects of DDT on neurobehaviour in birds are at least partially due to its ability

to bind to and activate or inactivate the estrogen and androgen receptors, respectively, that are present at high concentrations in the song centre and two other areas of the brain (the ICo and the septum; Gahr et al., 2001). Both the size of the ICo and its neurons, thought to play a role in copulation, vocal displays and antagonistic behaviour, can also be affected by circulating hormone levels (Gurney & Konishi, 1980). Indeed, in a recent study, exposure to DDT (15-175 µg/g) during the embryonic and early post hatching period was shown to alter the structure of the American robin brain, such that relative forebrain size (male) and absolute song nuclei (male) and ICo volumes (male and female) were significantly reduced with increasing DDT exposure when the animals were examined 2 years post exposure (Iwaniuk et al., 2006). Although stress and direct neurotoxicity could not be ruled out as causes of these changes, it seems likely that endocrine disruption played a role, as the size of other adjacent AR and ER negative areas of the brain were not affected by the exposure.

Female-female pairing, as occurred when gulls, albatrosses and geese were exposed to DDT and other pesticides, could also have been due to feminization of the brain. In this case, however, these seemingly altered preferences could also have been opportunistic responses to a lack of availability of males (seen commonly in other species) and here caused by biased sex ratios in the gulls (also an effect of the DDT; see section 2.3 of this chapter).

2.6.4.3 Other EDCs

Feminizing effects of other xenoestrogens on sexually selected neurobehavioral traits have also been observed in wild mammals. A study of polygamous deer mice developmentally exposed to the endocrine disrupting chemicals ethinylestradiol (EE2) or bisphenol A (BPA) showed that although there were no changes in external phenotype, sensory development, or adult circulating concentrations of testosterone or corticosterone, spatial learning abilities and exploratory behaviours were compromised. Moreover, both BPA-exposed and control females preferred the control males in preference to the exposed males (Jasarevic et al., 2011). Males of this species compete for mates by expanding their territorial range during the breeding season, thereby increasing their prospects of locating mates that are widely dispersed. This adult male spatial ability and exploratory behaviour requires both a seasonal increase in testosterone and prenatal exposure to the same hormone (Galea, Karaliers & Ossenkopp, 1996).

The mechanism underlying the effects of ethinylestradiol (EE2) and BPA is not known, but could be either a direct effect of these EDCs on brain development in the male pups, and/or due to a decreased maternal investment in the pups by the dam (as has been observed also in rodents; Palanza et al., 2002; Della Seta et al., 2008). These changes could also occur as a result of effects on the expression of estrogen receptor genes during neurodevelopment or as a result of suppression of fetal testosterone production at the time when the androgens from the testes normally masculinize the developing brain.

The results of this study in a wild mammal are supported by numerous studies in rodents in the laboratory in which estrogenic chemicals have been shown to influence neurobiology. For example, several studies indicate that exposure of the developing brain to phytoestrogens affects early sexual differentiation of the brain, by mimicking effects of estrogens on the size and neurochemistry of sexually dimorphic regions causing alterations in reproductive behaviour. These effects are sensitive to the timing and duration of the exposure and inconsistent results are often noted due to differences in methodology. Moreover, increasing evidence also suggests PBDE exposure can also influence reproductive behaviours in birds at environmentally relevant concentrations (Fernie et al., 2008). It has been suggested that these studies are of relevance to human babies consuming soy formula during the early postnatal period (reviewed in Dickerson & Gore, 2007).

PCBs do not appear to influence adult volume of the sexually dimorphic areas of the brain but they can influence numbers of nuclear hormone receptors in these sexually dimorphic brain regions of exposed rodents during early development. It is not clear what these changes mean in terms of the function of the brain in this case. In addition, it is not yet clear whether the PCB congeners have equivalent potential for disruption of the sexual differentiation of the brain. Despite this, laboratory studies have consistently shown that PCB exposure during early development affects adult female reproductive behaviour and a limited number of studies also report effects on the male (reviewed in Dickerson & Gore, 2007).

Increasing evidence now indicates that xenoestrogens can affect sexualization of the brain in fish in a general manner, and not only sexually dimorphic features. Further study of this area is needed both in wild populations of fish and in biomedical toxicology where the fish brain could be considered a good model for brain sexualisation in humans. Unlike in mammals and birds, the brain of fish is not permanently sexualised during early development, but is instead, highly susceptible to hormones throughout its life. Despite this unique difference between fish and other vertebrates, most of the hormones sustaining the neurobehavioral controls of the reproductive process are similar, if not identical. Moreover, as recently discovered in mammals and birds estrogen, and not androgen, receptors in male and female fish play a role in differentiation of the neural circuits that control male-specific behaviour. The masculinizing effect of testosterone on the brain is through its conversion to estrogen by brain aromatase, a highly sensitive target for endocrine disruptors (reviewed in Le Page et al., 2010).

2.6.5 Evidence for a common EDC mechanism of neurodevelopmental disruption for humans and wildlife

In many cases, the neurotoxicological outcomes of chemical exposures are similar in wildlife and in humans, adding weight of evidence to relationships between chemical exposure and neurodevelopmental disorders in humans (Basu & Head, 2010).

Unlike in humans, pollutant levels in the brains of wildlife species can be easily sampled and measured and can reach levels that are associated with neurotoxic damage in humans. There are reports in the literature of damaged brains and spinal cords in wild bald eagles and great blue herons in the USA and a strong association between these anomalies and exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, which was discovered at high levels in the birds. As early as 1915, lead-related neurological disorders were observed in horses and cattle living near industrial facilities. Moreover, before adverse neurological effects of mercury were seen in the human residents of the Great Lakes basin and in Minimata Bay (Japan), neurological effects were seen in local wildlife species through the 1950s and 1960s (Harada, 1995).

Wildlife can also provide important insights into mechanisms of neurotoxicity that may be important for human health. As one might expect from the high conservation of brain pituitary functions in vertebrates, neurohormones and neuropeptides controlling these tropic functions are well conserved and so the control of brain development by thyroid hormones and of reproductive behaviour by sex steroid hormones and GnRH neurons and neurotransmitters is similar amongst all vertebrates. Most of this work has been carried out in birds and fish, in which a diverse array of hormones have been shown to be involved in the stimulation of courtship and mating behaviour, including gonadal sex steroids produced locally within the brain, and neuropeptides.

2.6.6 Main messages

- Neurobehavioural disorders have increased in prevalence in human populations. The reasons for this are multiple and not understood.
- Despite this, the economic, societal and personal costs of this particular disease burden are high.
- There are some very strong datasets, for PCBs, showing that environmentally relevant exposures to these endocrine disrupting chemicals caused cognitive and behavioural deficits in humans.
- Studies of exposed wildlife provide important information on exposure levels, early and sub-clinical effects and clinical neurotoxicity of endocrine disrupting chemicals because the mechanisms underlying effects and the outcomes of exposures are often similar to those in humans. Wildlife data exist for some EDCs (e.g. PCBs) and potential EDCs (e.g. Mercury), but for other EDCs they are sparse or non-existent.
- Limited evidence shows that environmentally relevant exposures to some endocrine disrupting chemicals (mercury, bisphenol A, PCBs, PBDEs) could affect brain sexualisation, courtship behaviour and mate choice in some wildlife species, possibly leading to impacts at the population level.
- Chemical testing strategies do not routinely require evaluation of the ability of a chemical to produce developmental neurotoxic effects in a pre-market setting.
- New criteria for evidence are needed so that the scientific community and government agencies can focus their work and their funding on providing the most effective datasets required for regulation.

2.6.7 Scientific progress since 2002

Since the IPCS (2002) review on endocrine disruptors, the following advances have been made:

- Increased evidence for thyroid hormone mechanisms in brain disorders in humans and wildlife.
- Increased evidence of the great sensitivity of embryonic and postnatal development to EDCs when compared with adults.
- Increased number of studies showing a relationship between cognitive function and chemical exposures in humans. These studies however are often weakened by the nature of the study designs, and more prospective studies are warranted.
- Increased evidence for wildlife exposures to methylmercury and of effects on growth and development.
- First evidence of subtle effects of methylmercury and bisphenol A on reproductive behaviours of wildlife individuals that may be of relevance to populations.

2.6.8 Strength of evidence

There is sufficient evidence to conclude that published estimates of incidence and prevalence of some childhood neurobehavioural disorders have increased world wide over the past 10-20 years. Moreover, there is sufficient evidence to conclude that a number of factors, including environmental, contribute to the increases in autism spectrum disorders. There is also sufficient evidence to conclude that exposure to some industrial chemicals is plausibly related to the production of neurobehavioural disorders seen in both wildlife and humans. Exposures to lead, methylmercury, and PCBs represent strong cases in support of this, among others. There is sufficient evidence to conclude that PCBs can exert developmental neurotoxic effects in animals at doses that are similar to those of humans. More recent rodent studies of very low exposures to individual PCB congeners clearly make this point. There is sufficient evidence to conclude that specific PCB congeners and their metabolites can directly interfere with biological systems in rodents including thyroid hormone action and calcium regulation. There are limited data supporting an endocrine mechanism in the association of neurobehavioural disorders with some industrial chemicals. This is a challenging area that needs further focus. There are limited data to show that developmental exposure of some wildlife species to environmentally relevant concentrations of some chemicals can cause effects on brain sexualisation, leading to alterations in mate choice and courtship behaviours with outcomes that are relevant to populations. This area is important and needs further study.

2.6.9 References

Adkins-Regan E (2011). Neuroendocrine contributions to sexual partner preference in birds. *Frontiers in Neuroendocrinology,* 32(2):155-163.

Aguiar A, Eubig PA, Schantz SL (2010). Attention deficit hyperactivity disorder: A focused overview for children's evironmental health researchers. *Environmental Health Perspectives*.

American Phychiatric Association (2000). *Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision*. Washington DC, American Phychiatric Publishing.

Aronson SM (2005). The dancing cats of Minamata Bay. *Medicine and Health, Rhode Island,* 88(7):209.

Balthazart J (2011). Minireview: Hormones and human sexual orientation. *Endocrinology,* 152(8):2937-2947.

Barkley RA (1998). Attention-deficit hyperactivity disorder. *Scientific American,* 279(3):66-71.

Barr JF (1986). Population dynamics of the common loon gavia-immer associated with mercury-contaminated waters in northwestern Ontario Canada *Canadian Wildlife Service Occasional Paper,* 56:3-25.

Bastomsky CH (1974). Effects of a polychlorinated biphenyl mixture (Aroclor 1254) and DDT on biliary thyroxine excretion in rats. *Endocrinology,* 95:1150-1155.

Basu N, Head J (2010). Mammalian wildlife as complementary models in environmental neurotoxicology. *Neurotoxicology and Teratology,* 32(1):114-119.

Basu N, Scheuhammer AM, O'Brien M (2007). Polychlorinated biphenyls, organochlorinated pesticides, and polybrominated diphenyl ethers in the cerebral cortex of wild river otters (*Lontra canadensis*). *Environmental Pollution,* 149(1):25-30.

Basu N, Scheuhammer AM, Evans RD, O'Brien M, Chan HM (2007a). Cholinesterase and monoamine oxidase activity in relation to mercury levels in the cerebral cortex of wild river otters. *Human and Experimental Toxicology,* 26(3):213-220.

Basu N, Scheuhammer AM, Bursian SJ, Elliott J, Rouvinen-Watt K, Chan HM (2007b). Mink as a sentinel species in environmental health. *Environmental Research,* 103(1):130-144.

Basu N, Scheuhammer AM, Sonne C, Letcher RJ, Born EW, Dietz R (2009). Is dietary mercury of neurotoxicological concern to wild polar bears (*Ursus maritimus*)? *Environmental Toxicology and Chemistry,* 28(1):133-140.

Basu N, Scheuhammer AM, Rouvinen-Watt K, Evans RD, Trudeau VL, Chan LH (2010). In vitro and whole animal evidence that methylmercury disrupts GABAergic systems in discrete brain regions in captive mink. *Comparative Biochemistry and Physiology. Toxicology and Pharmacology,* 151(3):379-385.

Basu N, Scheuhammer AM, Rouvinen-Watt K, Grochowina N, Klenavic K, Evans RD, Chan HM (2006). Methylmercury impairs components of the cholinergic system in captive mink (*Mustela vison*). *Toxicological Sciences,* 91(1):202-209.

Basu N, Scheuhammer AM, Rouvinen-Watt K, Grochowina N, Evans RD, O'Brien M, Chan HM (2007c). Decreased N-methyl-D-aspartic acid (NMDA) receptor levels are associated with mercury exposure in wild and captive mink. *Neurotoxicology,* 28(3):587-593.

Beckvar N, Dillon TM, Read LB (2005). Approaches for linking whole-body fish tissue residues of mercury or DDT to biological effects thresholds. *Environmental Toxicology and Chemistry,* 24(8):2094-2105.

Bellinger D (2008). Environmental neurotoxicants and child development. *International Journal of Psychology,* 43(3-4):358-358.

Bemis JC, Seegal RF (1999). Polychlorinated biphenyls and methylmercury act synergistically to reduce rat brain dopamine content in vitro. *Environmental Health Perspectives,* 107(11):879-885.

Bernal J (2005). The significance of thyroid hormone transporters in the brain. *Endocrinology,* 146(4):1698-1700.

Berntssen MH, Aatland A, Handy RD (2003). Chronic dietary mercury exposure causes oxidative stress, brain lesions, and altered behaviour in Atlantic salmon (*Salmo salar*) parr. *Aquatic Toxicology,* 65(1):55-72.

Billon N, Jolicoeur C, Tokumoto Y, Vennstrom B, Raff M (2002). Normal timing of oligodendrocyte development depends on thyroid hormone receptor alpha 1 (TRalpha1). *EMBO Journal,* 21(23):6452-6460.

Borrelli E, Nestler EJ, Allis CD, Sassone-Corsi P (2008). Decoding the epigenetic language of neuronal plasticity. *Neuron,* 60(6):961-974.

Bouchard MF, Bellinger DC, Wright RO, Weisskopf MG (2010). Attention-deficit/hyperactivity disorder and urinary metabolites of organophosphate pesticides. *Pediatrics,* 125(6):e1270-1277.

Branchi I, Capone F, Alleva E, Costa LG (2003). Polybrominated diphenyl ethers: neurobehavioral effects following developmental exposure. *Neurotoxicology,* 24(3):449-462.

Branchi I, Capone F, Vitalone A, Madia F, Santucci D, Alleva E, Costa LG (2005). Early developmental exposure to BDE 99 or Aroclor 1254 affects neurobehavioural profile: interference from the administration route. *Neurotoxicology,* 26(2):183-192.

Braune BM, Mallory ML, Gilchrist HG (2006). Elevated mercury levels in a declining population of ivory gulls in the Canadian Arctic. *Marine Pollution Bulletin,* 52(8):978-982.

Breedlove SM (2010). Minireview: Organizational hypothesis: instances of the fingerpost. *Endocrinology,* 151(9):4116-4122.

Burgess NM, Meyer MW (2008). Methylmercury exposure associated with reduced productivity in common loons. *Ecotoxicology,* 17(2):83-91.

Carpenter DO (2006). Polychlorinated biphenyls (PCBs): routes of exposure and effects on human health. *Reviews on Environmental Health,* 21(1):1-23.

Chen YCJ, Guo YL, Hsu CC, Rogan WJ (1992). Cognitive-development of yu-cheng (oil disease) children prenatally exposed to heat-degraded PCBs. *JAMA,* 268(22):3213-3218.

Chevrier J, Eskenazi B, Bradman A, Fenster L, Barr DB (2007). Associations between prenatal exposure to polychlorinated biphenyls and neonatal thyroid-stimulating hormone levels in a Mexican-American population, Salinas Valley, California. *Environmental Health Perspectives,* 115(10):1490-1496.

Chevrier J, Harley KG, Bradman A, Gharbi M, Sjodin A, Eskenazi B (2010). Polybrominated diphenyl ether (PBDE) flame retardants and thyroid hormone during pregnancy. *Environmental Health Perspectives,* 118(10):1444-1449.

Coccini T, Randine G, Castoldi AF, Grandjean P, Ostendorp G, Heinzow B, 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(4):468-477.

Costa LG, Giordano G (2007). Developmental neurotoxicity of polybrominated diphenyl ether (PBDE) flame retardants. *Neurotoxicology,* 28(6):1047-1067.

Cranefield P, Federn W (1963). Paracelsus on Gioter and Cretinism: A Translation and Discussion of "De Struma, Vulgo Der Kropf. *Bulletin of the History of Medicine,* 37:463-471.

Crump KL, Trudeau VL (2009). Mercury-induced reproductive impairment in fish. *Environmental Toxicology and Chemistry,* 28(5):895-907.

Darnerud PO, Aune M, Larsson L, Hallgren S (2007). Plasma PBDE and thyroxine levels in rats exposed to Bromkal or BDE-47. *Chemosphere,* 67(9):S386-392.

Della Seta D, Farabollini F, Dessi-Fulgheri F, Fusani L (2008). Environmental-like exposure to low levels of estrogen affects sexual behavior and physiology of female rats. *Endocrinology,* 149(11):5592-5598.

Dickerson SM, Gore AC (2007). Estrogenic environmental endocrine-disrupting chemical effects on reproductive neuroendocrine function and dysfunction across the life cycle. *Reviews in Endocrine and Metabolic Disorders,* 8(2):143-159.

Dickerson SM, Cunningham SL, Gore AC (2011). Prenatal PCBs disrupt early neuroendocrine development of the rat hypothalamus. *Toxicology and Applied Pharmacology,* 252(1):36-46.

Dickerson SM, Cunningham SL, Patisaul HB, Woller MJ, Gore AC (2011). Endocrine disruption of brain sexual differentiation by developmental PCB exposure. *Endocrinology,* 152(2):581-594.

DiMaio S, Grizenko N, Joober R (2003). Dopamine genes and attention-deficit hyperactivity disorder: a review. *Journal of Psychiatry and Neuroscience,* 28(1):27-38.

Dingemans MM, van den Berg M, Westerink RH (2011). Neurotoxicity of brominated flame retardants: (in)direct effects of parent and hydroxylated polybrominated diphenyl ethers on the (developing) nervous system. *Environmental Health Perspectives,* 119(7):900-907.

Ehrhardt AA, Meyer-Bahlburg HF, Rosen LR, Feldman JF, Veridiano NP, Zimmerman I, McEwen BS (1985). Sexual orientation after prenatal exposure to exogenous estrogen. *Archives of Sexual Behavior,* 14(1):57-77.

Ellingsen DG, Efskind J, Haug E, Thomassen Y, Martinsen I, Gaarder PI (2000). Effects of low mercury vapour exposure on the thyroid function in chloralkali workers. *Journal of Applied Toxicology,* 20(6):483-489.

Eriksson P, Fischer C, Karlsson H, Fredriksson A (2003). Interaction between a brominated flame-retardant (PBBE 99) and an ortho-substituted PCB (PCB 52) enhances developmental neurotoxic effects. *Toxicological Sciences,* 72:323-324.

Eubig PA, Aguiar A, Schantz SL (2010). Lead and PCBs as risk factors for attention deficit/hyperactivity disorder. *Environmental Health Perspectives,* 118(12):1654-1667.

Evers DC, Savoy LJ, DeSorbo CR, Yates DE, Hanson W, Taylor KM, Siegel LS, Cooley JH, Jr., Bank MS, Major A, Munney K, Mower BF, Vogel HS, Schoch N, Pokras M, Goodale MW, Fair J (2008). Adverse effects from environmental mercury loads on breeding common loons. *Ecotoxicology,* 17(2):69-81.

Falk H (2003). International environmental health for the pediatrician: case study of lead poisoning. *Pediatrics,* 112(1 Pt 2):259-264.

Farabollini F, Porrini S, Della Seta D, Bianchi F, Dessi-Fulgheri F (2002). Effects of perinatal exposure to bisphenol A on sociosexual behavior of female and male rats. *Environmental Health Perspectives,* 110 Suppl 3:409-414.

Fernie KJ, Laird Shutt J, Ritchie IJ, Letcher RJ, Drouillard K, Bird DM (2006). Changes in the growth, but not the survival, of American kestrels (*Falco sparverius*) exposed to environmentally relevant polybrominated diphenyl ethers. *Journal of Toxicology and Environmental Health. Part A,* 69(16):1541-1554.

Fernie KJ, Shutt JL, Letcher RJ, Ritchie JI, Sullivan K, Bird DM (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. *Toxicological Sciences,* 102(1):171-178.

Fox DA, Opanashuk L, Zharkovsky A, Weiss B (2010). Gene-chemical interactions in the developing mammalian nervous system: Effects on proliferation, neurogenesis and differentiation. *Neurotoxicology,* 31(5):589-597.

Frederick P, Jayasena N. (2011). Altered pairing behaviour and reproductive success in white ibises exposed to environmentally relevant concentrations of methylmercury. Proceedings Biological sciences / The Royal Society 278(1713): 1851-1857.

Gahr M (2001). Distribution of sex steroid hormone receptors in the avian brain: Functional implications for neural sex differences and sexual behaviors. *Microscopy Research and Technique,* 55(1):1-11.

Galea LAM, Kavaliers M, Ossenkopp KP (1996). Sexually dimorphic spatial learning in meadow voles *Microtus pennsylvanicus* and deer mice *Peromyscus maniculatus*. *Journal of Experimental Biology,* 199(1):195-200.

Gauger KJ, Giera S, Sharlin DS, Bansal R, Iannacone E, Zoeller RT (2007). Polychlorinated biphenyls 105 and 118 form thyroid hormone receptor agonists after cytochrome P4501A1 activation in rat pituitary GH3 cells. *Environmental Health Perspectives,* 115(11):1623-1630.

Gee JR, Moser VC (2008). Acute postnatal exposure to brominated diphenylether 47 delays neuromotor ontogeny and alters motor activity in mice. *Neurotoxicology and Teratology,* 30(2):79-87.

Gee JR, Hedge JM, Moser VC (2008). Lack of alterations in thyroid hormones following exposure to polybrominated diphenyl ether 47 during a period of rapid brain development in mice. *Drug and Chemical Toxicology,* 31(2):245-254.

Giera S, Bansal R, Ortiz-Toro TM, Taub DG, Zoeller RT (2011). Individual polychlorinated biphenyl (PCB) congeners produce tissue- and gene-specific effects on thyroid hormone signaling during development. *Endocrinology,* 152(7):2909-2919.

Giesy JP, Kannan K (1998). Dioxin-like and non-dioxin-like toxic effects of polychlorinated biphenyls (PCBs): Implications for risk assessment. *Critical Reviews in Toxicology,* 28(6):511-569.

Goldey ES, Crofton KM (1998). Thyroxine replacement attenuates hypothyroxinemia, hearing loss, and motor deficits following developmental exposure to Aroclor 1254 in rats. *Toxicological Sciences,* 45(1):94-105.

Goldey ES, Kehn LS, Lau C, Rehnberg GL, Crofton KM (1995). Developmental exposure to polychlorinated-biphenyls (Aroclor-1254) reduces circulating thyroid-hormone concentrations and causes hearing deficits in rats. *Toxicology and Applied Pharmacology,* 135(1):77-88.

Gore AC (2008). Developmental programming and endocrine disruptor effects on reproductive neuroendocrine systems. *Frontiers in Neuroendocrinology,* 29(3):358-374.

Grandjean P, Murata K, Budtz-Jorgensen E, Weihe P (2004). Cardiac autonomic activity in methylmercury neurotoxicity: 14-year follow-up of a Faroese birth cohort. *Journal of Pediatrics,* 144(2):169-176.

Grandjean P, Weihe P, Burse VW, Needham LL, Storr-Hansen E, Heinzow B, Debes F, Murata K, Simonsen H, Ellefsen P, Budtz-Jorgensen E, Keiding N, White RF (2001). Neurobehavioral deficits associated with PCB in 7-year-old children prenatally exposed to seafood neurotoxicants. *Neurotoxicology and Teratology,* 23(4):305-317.

Gulledge CC, Deviche P (1997). Androgen control of vocal control region volumes in a wild migratory songbird (*Junco hyemalis*) is region and possibly age dependent. *Journal of Neurobiology,* 32(4):391-402.

Guo YL, Lambert GH, Hsu CC, Hsu MM (2004). Yucheng: health effects of prenatal exposure to polychlorinated biphenyls and dibenzofurans. *International Archives of Occupational and Environmental Health,* 77(3):153-158.

Gurney ME, Konishi M (1980). Hormone-induced sexual differentiation of brain and behavior in zebra finches. *Science,* 208(4450):1380-1383.

Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O'Heir CE, Mitchell ML, Hermos RJ, Waisbren SE, Faix JD, Klein RZ (1999). Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *New England Journal of Medicine,* 341(8):549-555.

Hallgren S, Darnerud PO (2002). Polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs) and chlorinated paraffins (CPs) in rats - testing interactions and mechanisms for thyroid hormone effects. *Toxicology,* 177(2-3):227-243.

Hallinger KK, Zabransky DJ, Kazmer KA, Cristol DA (2010). Birdsong differs between mercury-polluted and reference sites. *Auk,* 127(1):156-161.

Hammerschmidt CR, Sandheinrich MB, Wiener JG, Rada RG (2002). Effects of dietary methylmercury on reproduction of fathead minnows. *Environmental Science and Technology,* 36(5):877-883.

Hampson E, Ellis CL, Tenk CM (2008). On the relation between 2D:4D and sex-dimorphic personality traits. *Archives of Sexual Behavior,* 37(1):133-144.

Harada M (1995). Minamata Disease - Methylmercury Poisoning in Japan Caused by Environmental-Pollution. *Critical Reviews in Toxicology,* 25(1):1-24.

Henley CL, Nunez AA, Clemens LG (2009). Estrogen treatment during development alters adult partner preference and reproductive behavior in female laboratory rats. *Hormones and Behavior,* 55(1):68-75.

Henley CL, Nunez AA, Clemens LG (2011). Hormones of choice: the neuroendocrinology of partner preference in animals. *Frontiers in Neuroendocrinology,* 32(2):146-154.

Hentschel T, Hruschka F, Priester M (2003). *Artisanal and Small-Scale Mining. Challenges and Opportunities*. International Institute for Environment and Development.

Herbstman JB, Sjodin A, Kurzon M, Lederman SA, Jones RS, Rauh V, Needham LL, Tang D, Niedzwiecki M, Wang RY, Perera F (2010). Prenatal exposure to PBDEs and neurodevelopment. *Environmental Health Perspectives,* 118(5):712-719.

Herr DW, Goldey ES, Crofton KM (1996). Developmental exposure to Aroclor 1254 produces low-frequency alterations in adult rat brainstem auditory evoked responses. *Fundamental and Applied Toxicology,* 33(1):120-128.

Hightower JM, O'Hare A, Hernandez GT (2006). Blood mercury reporting in NHANES: identifying Asian, Pacific Islander, Native American, and multiracial groups. *Environmental Health Perspectives,* 114(2):173-175.

Ikonomou MG, Rayne S, Addison RF (2002). Exponential increases of the brominated flame retardants, polybrominated diphenyl ethers, in the Canadian Arctic from 1981 to 2000. *Environmental Science and Technology,* 36(9):1886-1892.

Iwaniuk AN, Koperski DT, Cheng KM, Elliott JE, Smith LK, Wilson LK, Wylie DR (2006). The effects of environmental exposure to DDT on the brain of a songbird: changes in structures associated with mating and song. *Behavioural Brain Research,* 173(1):1-10.

Iwasaki T, Miyazaki W, Takeshita A, Kuroda Y, Koibuchi N (2002). Polychlorinated biphenyls suppress thyroid hormone-induced transactivation. *Biochemical and Biophysical Research Communications,* 299(3):384-388.

Jacobson JL, Jacobson SW (1996). Intellectual impairment in children exposed to polychlorinated biphenyls in utero. *New England Journal of Medicine,* 335(11):783-789.

Jacobson JL, Jacobson SW (2003). Prenatal exposure to polychlorinated biphenyls and attention at school age. *Journal of Pediatrics,* 143(6):780-788.

Jasarevic E, Sieli PT, Twellman EE, Welsh TH, Jr., Schachtman TR, Roberts RM, Geary DC, Rosenfeld CS (2011). Disruption of adult expression of sexually selected traits by developmental exposure to bisphenol A. *Proceedings of the National Academy of Sciences of the United States of America,* 108(28):11715-11720.

Johansen P, Muir D, Asmund G, Riget F (2004). Human exposure to contaminants in the traditional Greenland diet. *Science of the Total Environment,* 331(1-3):189-206.

Johnson-Restrepo B, Kannan K (2009). An assessment of sources and pathways of human exposure to polybrominated diphenyl ethers in the United States. *Chemosphere,* 76(4):542-548.

Jugan ML, Levi Y, Blondeau JP (2010). Endocrine disruptors and thyroid hormone physiology. *Biochemical Pharmacology,* 79(7):939-947.

Kawai K, Nozaki T, Nishikata H, Aou S, Takii M, Kubo C (2003). Aggressive behavior and serum testosterone concentration during the maturation process of male mice: The effects of fetal exposure to bisphenol A. *Environmental Health Perspectives,* 111(2):175-178.

Khan IA, Thomas P (1997). Aroclor 1254-induced alterations in hypothalamic monoamine metabolism in the Atlantic croaker (*Micropogonias undulatas*): correlation with pituitary gonadotropin release. *Neurotoxicology,* 18(2):553-560.

Khan IA, Thomas P (2001). Disruption of neuroendocrine control of luteinizing hormone secretion by aroclor 1254 involves inhibition of hypothalamic tryptophan hydroxylase activity. *Biology of Reproduction,* 64(3):955-964.

Khan IA, Thomas P (2006). PCB congener-specific disruption of reproductive neuroendocrine function in Atlantic croaker. *Marine Environmental Research,* 62 Suppl:S25-28.

Khan SA, Faraone SV (2006). The genetics of ADHD: a literature review of 2005. *Current Psychiatry Reports,* 8(5):393-397.

Kirley A, Hawi Z, Daly G, McCarron M, Mullins C, Millar N, Waldman I, Fitzgerald M, Gill M (2002). Dopaminergic system genes in ADHD: toward a biological hypothesis. *Neuropsychopharmacology,* 27(4):607-619.

Kodavanti PR, Ward TR, Derr-Yellin EC, Mundy WR, Casey AC, Bush B, Tilson HA (1998). Congener-specific distribution of polychlorinated biphenyls in brain regions, blood, liver, and fat of adult rats following repeated exposure to Aroclor 1254. *Toxicology and Applied Pharmacology,* 153(2):199-210.

Kodavanti PR, Coburn CG, Moser VC, MacPhail RC, Fenton SE, Stoker TE, Rayner JL, Kannan K, Birnbaum LS (2010). Developmental exposure to a commercial PBDE mixture, DE-71: neurobehavioral, hormonal, and reproductive effects. *Toxicological Sciences,* 116(1):297-312.

Koibuchi N, Iwasaki T (2006). Regulation of brain development by thyroid hormone and its modulation by environmental chemicals. *Endocrine Journal,* 53(3):295-303.

Kubo K, Arai O, Omura M, Watanabe R, Ogata R, Aou S (2003). Low dose effects of bisphenol A on sexual differentiation of the brain and behavior in rats. *Neuroscience Research,* 45(3):345-356.

Kuehn BM (2010). Increased risk of ADHD associated with early exposure to pesticides, PCBs. *JAMA,* 304(1):27-28.

Kuriyama SN, Wanner A, Fidalgo-Neto AA, Talsness CE, Koerner W, Chahoud I (2007). Developmental exposure to low-dose PBDE-99: tissue distribution and thyroid hormone levels. *Toxicology,* 242(1-3):80-90.

LaFranchi SH (2010). Newborn screening strategies for congenital hypothyroidism: an update. *Journal of Inherited Metabolic Disease,* 33(Suppl 2):S225-233.

Landrigan PJ, Goldman LR (2011a). Children's vulnerability to toxic chemicals: a challenge and opportunity to strengthen health and environmental policy. *Health Affairs,* 30(5):842-850.

Landrigan PJ, Goldman LR (2011b). Protecting children from pesticides and other toxic chemicals. *Journal of Exposure Science and Environmental Epidemiology,* 21(2):119-120.

Le Page Y, Diotel N, Vaillant C, Pellegrini E, Anglade I, Merot Y, Kah O (2010). Aromatase, brain sexualization and plasticity: the fish paradigm. *European Journal of Neuroscience,* 32(12):2105-2115.

Lema SC, Dickey JT, Schultz IR, Swanson P (2006). Disruption of the fish thyroid axis by Polybrominated diphenyl ether (PBDE) flame retardants. *Integrative and Comparative Biology,* 46:E83-E83.

Lema SC, Dickey JT, Schultz IR, Swanson P (2008). Dietary exposure to 2,2',4,4'-tetrabromodiphenyl ether (PBDE-47) alters thyroid status

and thyroid hormone-regulated gene transcription in the pituitary and brain. *Environmental Health Perspectives,* 116(12):1694-1699.

Lema SC, Dickey JT, Schultz IR, Swanson P (2009). Thyroid hormone regulation of mRNAs encoding thyrotropin beta-subunit, glycoprotein alpha-subunit, and thyroid hormone receptors alpha and beta in brain, pituitary gland, liver, and gonads of an adult teleost, *Pimephales promelas*. *Journal of Endocrinology,* 202(1):43-54.

Lilienthal H, Hack A, Roth-Harer A, Grande SW, Talsness CE (2006). Effects of developmental exposure to 2,2 ,4,4 ,5-pentabromodiphenyl ether (PBDE-99) on sex steroids, sexual development, and sexually dimorphic behavior in rats. *Environmental Health Perspectives,* 114(2):194-201.

Liu YW, Chan WK (2002). Thyroid hormones are important for embryonic to larval transitory phase in zebrafish. *Differentiation,* 70(1):36-45.

Longnecker MP, Gladen BC, Patterson DG, Jr., Rogan WJ (2000). Polychlorinated biphenyl (PCB) exposure in relation to thyroid hormone levels in neonates. *Epidemiology,* 11(3):249-254.

Manzo L, Castoldi AF, Coccini T, Prockop LD (2001). Assessing effects of neurotoxic pollutants by biochemical markers. *Environmental Research,* 85(1):31-36.

Maranduba CM, Friesema EC, Kok F, Kester MH, Jansen J, Sertie AL, Passos-Bueno MR, Visser TJ (2006). Decreased cellular uptake and metabolism in Allan-Herndon-Dudley syndrome (AHDS) due to a novel mutation in the MCT8 thyroid hormone transporter. *Journal of Medical Genetics,* 43(5):457-460.

Mariussen E, Fonnum F (2006). Neurochemical targets and behavioral effects of organohalogen compounds: An update. *Critical Reviews in Toxicology,* 36(3):253-289.

Marks AR, Harley K, Bradman A, Kogut K, Barr DB, Johnson C, Calderon N, Eskenazi B (2010). Organophosphate pesticide exposure and attention in young Mexican-American children: the CHAMACOS study. *Environmental Health Perspectives,* 118(12):1768-1774.

Mattson SN, Crocker N, Nguyen TT (2011). Fetal alcohol spectrum disorders: neuropsychological and behavioral features. *Neuropsychology Review,* 21(2):81-101.

McCarthy MM (2009). The two faces of estradiol: effects on the developing brain. *Neuroscientist,* 15(6):599-610.

McDonald ME, Paul JF (2010). Timing of increased autistic disorder cumulative incidence. *Environmental Science and Technology,* 44(6):2112-2118.

McLachlan JA (2001). Environmental signaling: What embryos and evolution teach us about endocrine disrupting chemicals. *Endocrine Reviews,* 22(3):319-341.

Mergler D, Anderson HA, Chan LH, Mahaffey KR, Murray M, Sakamoto M, Stern AH (2007). Methylmercury exposure and health effects in humans: a worldwide concern. *Ambio,* 36(1):3-11.

Metzdorf R, Gahr M, Fusani L (1999). Distribution of aromatase, estrogen receptor, and androgen receptor mRNA in the forebrain of songbirds and nonsongbirds. *Journal of Comparative Neurology,* 407(1):115-129.

Miller MD, Crofton KM, Rice DC, Zoeller RT (2009). Thyroid-disrupting chemicals: interpreting upstream biomarkers of adverse outcomes. *Environmental Health Perspectives,* 117(7):1033-1041.

Miyazaki W, Iwasaki T, Takeshita A, Kuroda Y, Koibuchi N (2004). Polychlorinated biphenyls suppress thyroid hormone receptor-mediated transcription through a novel mechanism. *Journal of Biological Chemistry,* 279(18):18195-18202.

Miyazaki W, Iwasaki T, Takeshita A, Tohyama C, Koibuchi N (2008). Identification of the functional domain of thyroid hormone receptor responsible for polychlorinated biphenyl-mediated suppression of its action in vitro. *Environmental Health Perspectives,* 116(9):1231-1236.

Needleman H (2009). Low level lead exposure: history and discovery. *Annals of Epidemiology,* 19(4):235-238.

Nweke OC, Sanders WH, 3rd. (2009). Modern environmental health hazards: a public health issue of increasing significance in Africa. *Environmental Health Perspectives,* 117(6):863-870.

Oosthuizen J, Ehrlich R (2001). The impact of pollution from a mercury processing plant in KwaZulu-Natal, South Africa, on the health of fish-eating communities in the area: an environmental health risk assessment. *International Journal of Environmental Health Research,* 11(1):41-50.

Palanza PL, Howdeshell KL, Parmigiani S, vom Saal FS (2002). Exposure to a low dose of bisphenol A during fetal life or in adulthood alters maternal behavior in mice. *Environmental Health Perspectives,* 110 Suppl 3:415-422.

Park HY, Park JS, Sovcikova E, Kocan A, Linderholm L, Bergman A, Trnovec T, Hertz-Picciotto I (2009). Exposure to hydroxylated polychlorinated biphenyls (OH-PCBs) in the prenatal period and subsequent neurodevelopment in eastern Slovakia. *Environmental Health Perspectives,* 117(10):1600-1606.

Patandin S, Lanting CI, Mulder PG, Boersma ER, Sauer PJ, Weisglas-Kuperus N (1999). Effects of environmental exposure to polychlorinated biphenyls and dioxins on cognitive abilities in Dutch children at 42 months of age. *Journal of Pediatrics,* 134(1):33-41.

Pedersen MB, Hansen JC, Mulvad G, Pedersen HS, Gregersen M, Danscher G (1999). Mercury accumulations in brains from populations exposed to high and low dietary levels of methyl mercury. Concentration, chemical form and distribution of mercury in brain samples from autopsies. *International Journal of Circumpolar Health,* 58(2):96-107.

Pessah IN, Cherednichenko G, Lein PJ (2010). Minding the calcium store: Ryanodine receptor activation as a convergent mechanism of PCB toxicity. *Pharmacology & Therapeutics,* 125(2):260-285.

Pilsner JR, Lazarus AL, Nam DH, Letcher RJ, Sonne C, Dietz R, Basu N (2010). Mercury-associated DNA hypomethylation in polar bear brains via the LUminometric Methylation Assay: a sensitive method to study epigenetics in wildlife. *Molecular Ecology,* 19(2):307-314.

Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA (2007). The worldwide prevalence of ADHD: a systematic review and metaregression analysis. *The American journal of psychiatry,* 164(6):942-948.

Porrini S, Belloni V, Della Seta D, Farabollini F, Giannelli G, Dessi-Fulgheri F (2005). Early exposure to a low dose of bisphenol A affects socio-sexual behavior of juvenile female rats. *Brain Research Bulletin,* 65(3):261-266.

Riccio CA, Avila L, Ash MJ (2010). Pesticide poisoning in a preschool child: a case study examining neurocognitive and neurobehavioral effects. *Applied Neuropsychology,* 17(2):153-159.

Rice CD (2007). Prevalence of autism spectrum disorders--autism and developmental disabilities monitoring network, six sites, United States, 2000. *MMWR Surveillance Summaries,* 56(1):1-11.

Riters LV, Teague DP (2003). The volumes of song control nuclei, HVC and lMAN, relate to differential behavioral responses of female European starlings to male songs produced within and outside of the breeding season. *Brain Research,* 978(1-2):91-98.

Riters LV, Eens M, Pinxten R, Duffy DL, Balthazart J, Ball GF (2000). Seasonal changes in courtship song and the medial preoptic area in male European starlings (*Sturnus vulgaris*). *Hormones and Behavior,* 38(4):250-261.

Roegge CS, Wang VC, Powers BE, Klintsova AY, Villareal S, Greenough WT, Schantz SL (2004). Motor impairment in rats exposed

to PCBs and methylmercury during early development. *Toxicological Sciences,* 77(2):315-324.

Roze E, Meijer L, Bakker A, Van Braeckel KN, Sauer PJ, Bos AF (2009). Prenatal exposure to organohalogens, including brominated flame retardants, influences motor, cognitive, and behavioral performance at school age. *Environmental Health Perspectives,* 117(12):1953-1958.

Rubin BS, Lenkowski JR, Schaeberle CM, Vandenberg LN, Ronsheim PM, Soto AM (2006). Evidence of altered brain sexual differentiation in mice exposed perinatally to low, environmentally relevant levels of bisphenol A. *Endocrinology,* 147(8):3681-3691.

Rutkiewicz J, Nam DH, Cooley T, Neumann K, Padilla IB, Route W, Strom S, Basu N (2011). Mercury exposure and neurochemical impacts in bald eagles across several Great Lakes states. *Ecotoxicology,* 20(7):1669-1676.

Sandheinrich MB, Miller KM (2006). Effects of dietary methylmercury on reproductive behavior of fathead minnows (*Pimephales promelas*). *Environmental Toxicology and Chemistry,* 25(11):3053-3057.

Savornin O, Niang K, Diouf A (2007). *Artisanal mining in the Tambacounda region of Senegal*. Kedougou, Senegal, Blacksmith Institute.

Schantz SL, Widholm JJ, Rice DC (2003). Effects of PCB exposure on neuropsychological function in children. *Environmental Health Perspectives,* 111(3):357-576.

Schettler T (2001). Toxic threats to neurologic development of children. *Environmental Health Perspectives,* 109 Suppl 6:813-816.

Scheuhammer AM, Meyer MW, Sandheinrich MB, Murray MW (2007). Effects of environmental methylmercury on the health of wild birds, mammals, and fish. *Ambio,* 36(1):12-18.

Schreiber T, Gassmann K, Gotz C, Hubenthal U, Moors M, Krause G, Merk HF, Nguyen NH, Scanlan TS, Abel J, Rose CR, Fritsche E (2010). Polybrominated diphenyl ethers induce developmental neurotoxicity in a human in vitro model: evidence for endocrine disruption. *Environmental Health Perspectives,* 118(4):572-578.

Schwartz CE, May MM, Carpenter NJ, Rogers RC, Martin J, Bialer MG, Ward J, Sanabria J, Marsa S, Lewis JA, Echeverri R, Lubs HA, Voeller K, Simensen RJ, Stevenson RE (2005). Allan-Herndon-Dudley syndrome and the monocarboxylate transporter 8 (MCT8) gene. *American Journal of Human Genetics,* 77(1):41-53.

Seegal RF (1996). Epidemiological and laboratory evidence of PCB-induced neurotoxicity. *Critical Reviews in Toxicology,* 26(6):709-737.

Sharlin DS, Tighe D, Gilbert ME, Zoeller RT (2008). The balance between oligodendrocyte and astrocyte production in major white matter tracts is linearly related to serum total thyroxine. *Endocrinology,* 149(5):2527-2536.

Smith CC, Taylor HS (2007). Xenoestrogen exposure imprints expression of genes (Hoxa10) required for normal uterine development. *FASEB Journal,* 21(1):239-246.

Sonne C, Dietz R, Leifsson PS, Asmund G, Born EW, Kirkegaard M (2007). Are liver and renal lesions in East Greenland polar bears (*Ursus maritimus*) associated with high mercury levels? *Environmental Health,* 6:11.

Stewart P, Reihman J, Lonky E, Darvill T, Pagano J (2000). Prenatal PCB exposure and neonatal behavioral assessment scale (NBAS) performance. *Neurotoxicology and Teratology,* 22(1):21-29.

Stewart P, Darvill T, Lonky E, Reihman J, Pagano J, Bush B (1999). Assessment of prenatal exposure to PCBs from maternal consumption of Great Lakes fish: an analysis of PCB pattern and concentration. *Environmental Research,* 80(2 Pt 2):S87-S96.

Stewart P, Reihman J, Gump B, Lonky E, Darvill T, Pagano J (2005). Response inhibition at 8 and 9 1/2 years of age in children prenatally exposed to PCBs. *Neurotoxicology and Teratology,* 27(6):771-780.

Stewart P, Fitzgerald S, Reihman J, Gump B, Lonky E, Darvill T, Pagano J, Hauser P (2003a). Prenatal PCB exposure, the corpus callosum, and response inhibition. *Environmental Health Perspectives,* 111(13):1670-1677.

Stewart PW, Reihman J, Lonky EI, Darvill TJ, Pagano J (2003b). Cognitive development in preschool children prenatally exposed to PCBs and MeHg. *Neurotoxicology and Teratology,* 25(1):11-22.

Stewart PW, Lonky E, Reihman J, Pagano J, Gump BB, Darvill T (2008). The relationship between prenatal PCB exposure and intelligence (IQ) in 9-year-old children. *Environmental Health Perspectives,* 116(10):1416-1422.

Takser L, Mergler D, Baldwin M, de Grosbois S, Smargiassi A, Lafond J (2005). Thyroid hormones in pregnancy in relation to environmental exposure to organochlorine compounds and mercury. *Environmental Health Perspectives,* 113(8):1039-1045.

Tanabe S, Ramu K, Isobe T, Takahashi S (2008). Brominated flame retardants in the environment of Asia-Pacific: an overview of spatial and temporal trends. *Journal of Environmental Monitoring,* 10(2):188-197.

Timme-Laragy AR, Levin ED, Di Giulio RT (2006). Developmental and behavioral effects of embryonic exposure to the polybrominated diphenylether mixture DE-71 in the killifish (*Fundulus heteroclitus*). *Chemosphere,* 62(7):1097-1104.

Toms LML, Harden F, Paepke O, Hobson P, Ryan JJ, Mueller JF (2008). Higher accumulation of polybrominated diphenyl ethers in infants than in adults. *Environmental Science and Technology,* 42(19):7510-7515.

Trasande L, Landrigan PJ, Schechter C (2005). Public health and economic consequences of methyl mercury toxicity to the developing brain. *Environmental Health Perspectives,* 113(5):590-596.

Trasande L, Schechter CB, Haynes KA, Landrigan PJ (2006). Mental retardation and prenatal methylmercury toxicity. *American Journal of Industrial Medicine,* 49(3):153-158.

Vahter M (2008). Health effects of early life exposure to arsenic. *Basic & Clinical Pharmacology & Toxicology,* 102(2):204-211.

van Straaten P (2000). Human exposure to mercury due to small scale gold mining in northern Tanzania. *Science of the Total Environment,* 259(1-3):45-53.

Viberg H (2009a). Exposure to polybrominated diphenyl ethers 203 and 206 during the neonatal brain growth spurt affects proteins important for normal neurodevelopment in mice. *Toxicological Sciences,* 109(2):306-311.

Viberg H (2009b). Neonatal ontogeny and neurotoxic effect of decabrominated diphenyl ether (PBDE 209) on levels of synaptophysin and tau. *International Journal of Developmental Neuroscience,* 27(5):423-429.

Viberg H, Fredriksson A, Eriksson P (2003). Neonatal exposure to polybrominated diphenyl ether (PBDE 153) disrupts spontaneous behaviour, impairs learning and memory, and decreases hippocampal cholinergic receptors in adult mice. *Toxicology and Applied Pharmacology,* 192(2):95-106.

Viberg H, Fredriksson A, 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. *Environmental Toxicology and Pharmacology,* 17(2):61-65.

Viberg H, Mundy W, Eriksson P (2008). Neonatal exposure to decabrominated diphenyl ether (PBDE 209) results in changes in BDNF, CaMKII and GAP-43, biochemical substrates of neuronal survival, growth, and synaptogenesis. *Neurotoxicology,* 29(1):152-159.

Visser WE, Jansen J, Friesema EC, Kester MH, Mancilla E, Lundgren J, van der Knaap MS, Lunsing RJ, Brouwer OF, Visser TJ (2009).

Novel pathogenic mechanism suggested by ex vivo analysis of MCT8 (SLC16A2) mutations. *Human Mutation,* 30(1):29-38.

Voorspoels S, Covaci A, Lepom P, Escutenaire S, Schepens P (2006a). Remarkable findings concerning PBDEs in the terrestrial top-predator red fox (*Vulpes vulpes*). *Environmental Science and Technology,* 40(9):2937-2943.

Voorspoels S, Covaci A, Lepom P, Jaspers VL, Schepens P (2006b). Levels and distribution of polybrominated diphenyl ethers in various tissues of birds of prey. *Environmental Pollution,* 144(1):218-227.

Vreugdenhil HJ, Van Zanten GA, Brocaar MP, Mulder PG, Weisglas-Kuperus N (2004). Prenatal exposure to polychlorinated biphenyls and breastfeeding: opposing effects on auditory P300 latencies in 9-year-old Dutch children. *Developmental Medicine and Child Neurology,* 46(6):398-405.

Walkowiak J, Wiener JA, Fastabend A, Heinzow B, Kramer U, Schmidt E, Steingruber HJ, Wundram S, Winneke G (2001). Environmental exposure to polychlorinated biphenyls and quality of the home environment: effects on psychodevelopment in early childhood. *Lancet,* 358(9293):1602-1607.

Weihe P, Hansen JC, Murata K, Debes F, Jorgensen P, Steuerwald U, White RF, Grandjean P (2002). Neurobehavioral performance of Inuit children with increased prenatal exposure to methylmercury. *International Journal of Circumpolar Health,* 61(1):41-49.

Weis JS (2009). Reproductive, developmental, and neurobehavioral effects of methylmercury in fishes. *Journal of Environmental Science and Health, Part C: Environmental Carcinogenesis & Ecotoxicology Reviews,* 27(4):212-225.

Weiss B, Landrigan PJ (2000). The developing brain and the environment: an introduction. *Environmental Health Perspectives,* 108 Suppl 3:373-374.

WHO (2011). Toxicological and Health Aspects of Bisphenol A. Joint FAO/WHO expert meeting to review toxicological and health aspects of bisphenol A: final report, including report of stakeholder meeting on bisphenol A, 1-5 November 2010, Ottawa, Canada. World Health Organization, Geneva, Switzerland.

WHO/CEHA (2003). *A review of literature on health environments for children in the Eastern Mediteranean Region. Status of childhood lead exposure (Draft 1)*. Geneva, World Health Organisation.

Wilhelm M, Ranft U, Kramer U, Wittsiepe J, Lemm F, Furst P, Eberwein G, Winneke G (2008). Lack of neurodevelopmental adversity by prenatal exposure of infants to current lowered PCB levels: comparison of two German birth cohort studies. *Journal of Toxicology and Environmental Health. Part A,* 71(11-12):700-702.

Williams GR (2008). Neurodevelopmental and neurophysiological actions of thyroid hormone. *Journal of Neuroendocrinology,* 20(6):784-794.

Wing L, Yeates SR, Brierley LM, Gould J (1976). The prevalence of early childhood autism: comparison of administrative and epidemiological studies. *Psychological Medicine,* 6(1):89-100.

Winneke G, Bucholski A, Heinzow B, Kramer U, Schmidt E, Walkowiak J, Wiener JA, Steingruber HJ (1998). Developmental neurotoxicity of polychlorinated biphenyls (PCBS): cognitive and psychomotor functions in 7-month old children. *Toxicology Letters,* 102-103:423-428.

Xu X, Nembhard WN, Kan H, Kearney G, Zhang ZJ, Talbott EO (2011). Urinary trichlorophenol levels and increased risk of attention deficit hyperactivity disorder among US school-aged children. *Occupational and Environmental Medicine,* 68(8):557-561.

Yolton K, Xu Y, Strauss D, Altaye M, Calafat AM, Khoury J (2011). Prenatal exposure to bisphenol A and phthalates and infant neurobehavior. *Neurotoxicology and Teratology,* 33(5):558-566.

Zala SM, Penn DJ (2004). Abnormal behaviours induced by chemical pollution: a review of the evidence and new challenges. *Animal Behaviour,* 68:649-664.

Zhou T, Taylor MM, DeVito MJ, Crofton KA (2002). Developmental exposure to brominated diphenyl ethers results in thyroid hormone disruption. *Toxicological Sciences,* 66(1):105-116.

Zoeller RT, Rovet J (2004). Timing of thyroid hormone action in the developing brain: clinical observations and experimental findings. *Journal of Neuroendocrinology,* 16(10):809-818.

Zoeller RT, Dowling AL, Vas AA (2000). Developmental exposure to polychlorinated biphenyls exerts thyroid hormone-like effects on the expression of RC3/neurogranin and myelin basic protein messenger ribonucleic acids in the developing rat brain. *Endocrinology,* 141(1):181-189.