2.5 Endocrine disruptors and thyroid-related disorders and diseases

2.5.1 Overview of thyroid-related disorders and diseases in humans and wildlife and evidence for endocrine disruption

Thyroid diseases and disorders in humans (e.g. congenital hypothyroidism and adult autoimmune thyroid disease) have increased in incidence over the past several decades, such that the burden of thyroid disease is approximately two billion people worldwide.

- **Thyroid diseases and disorders represent a particularly high and increasing disease burden in children and adolescents** in several countries in which they have been studied (McGrogan et al., 2008).
- **Between 6-10% of adults have a thyroid disease or disorder.** Hypothyroidism is the most common thyroid disorder and is six times more common in women than men (Vanderpump, Turnbridge & French, 1995)
- **Population-wide testing of thyroid function in the absence of suggestive clinical features reveals a great proportion of "mild" thyroid abnormalities that have most likely gone unrecognized.** These studies suggest that there may be many more adults with undiagnosed thyroid conditions than is currently appreciated (e.g. Canaris et al., 2000).
- Slight decreases in thyroid function - sometimes referred to as "subclinical" or mild hypothyroidism - may have adverse health consequences (elevated cholesterol levels, heart disease and diabetes), especially over the long term and during pregnancy.

Both genetic and environmental factors play a role in thyroid health. However, observations in laboratory animals and wildlife suggest that exposure to endocrine disruptors, particularly during fetal life, could also play a role. Alongside the human health trends, studies describing thyroid dysfunctions in wildlife also exist. Sometimes, these wildlife observations are associated with exposures to contaminants. Examples include:

- **Relationships between body burden of persistent organic pollutants (PCBs, PBDEs and organochlorine pesticides) and thyroid-related effects in marine mammals;** in seals (Brouwer., 1989; Hall, Kalantzi & Thomas, 2003; Hall & Thomas, 2007; Routti et al., 2008), sea lions (Debier et al., 2005), beluga whales inhabiting the St. Lawrence estuary (DeGuise et al., 1995), the harbour porpoise (Schnitzler et al., 2008), and polar bear (Braathen et al., 2004, Skaare et al., 2001).
- **Significant thyroid disruption in monitoring studies of birds in the Great Lakes, Barents Sea, Tokyo Bay, linked with EDC (PBDE and PCB) burdens** (Scanes & McNabb, 2003; Verreault et al., 2004; Saita et al., 2004).
- **Thyroid disruption in salmonid fish living in heavily polluted regions of the Great Lakes in the United States during the 1970s and 1980s and, more recently, in mummichogs in New Jersey and San Francisco Bay** (reviewed in Jobling & Tyler, 2003; Zhou et al., 2000; Brar et al., 2010). Effects in mummichogs were positively correlated with PCB concentrations measured in the livers of the fish.

Hormonal mechanisms underlying thyroid disorders and diseases

The thyroid gland is located at the base of the throat and straddles the trachea. When it becomes physically enlarged in some diseases, it is visible to the eye or can be palpated (goitre). The major product of the thyroid gland is "thyroxine" (tetraiodothyronine, T_4). However, T_4 is not considered to be the most active form of the hormone; rather, it is converted to tri-iodothyronine (T_3), which then acts on the thyroid hormone receptor (TR) in cells.

Thyroid function itself is controlled by "Thyroid-Stimulating Hormone" (TSH, or "thyrotropin"). TSH is a large protein hormone secreted from the pituitary gland that binds to specific membrane receptors on thyroid cells and activates a biochemical pathway that stimulates thyroid hormone production and secretion (Taurog, 2004). The amount of TSH stimulation required to maintain blood levels of thyroid hormone within a "normal" range is controlled by a negative feedback relationship between serum T_4 and serum TSH (Larsen, Silva & Kaplan, 1981). The negative feedback action of T_4 occurs both at the level of the hypothalamus (Vella & Hollenberg 2009; Hollenberg 2008; Greer et al., 1993; Koller et al., 1987; Aizawa & Greer 1981) and pituitary (Wan, Farboud & Privalsky, 2005; Hodin et al., 1989; Chin & Carr, 1987; Carr, Need & Chin, 1987). Thus, under normal conditions, there is a negative correlation between serum levels of T_4 (specifically "free" T_4) and serum TSH.

For this reason, blood levels of T_4 and TSH form the principle clinical measures of thyroid function and disease. So-called "reference" ranges are developed for human populations because there are slight differences in the set-point around which thyroid hormone is regulated in different races, ethnicities and in pregnancy. These reference ranges are generated from a large sample of the population that is without other measures of thyroid disease (symptoms or the presence of anti-thyroid antibodies) (Haddow et al., 2004; Surks, 1991). Reference ranges have been developed for different populations (e.g. Zarkovic et al., 2011), for the different periods of pregnancy (Haddow et al., 2004), even for twin versus singleton pregnancy (Haddow, Palomaki & McClain, 2006), and for preterm versus term birth (Clark et al., 2001; Adams et al., 1995).

Thyroid hormones are important for normal development of the human brain (Bernal, 2007; 2011; Oerbeck et al., 2007), lungs (van Tuyl et al., 2004; Bizzarro & Gross, 2004), heart

(Stoykov et al., 2006; Grover, Mellstom & Malm, 2005; Danzi, Dubon & Klein, 2005), and other organs. Moreover thyroid hormones induce metamorphosis in some fish (Yamano et al., 1994) and in frogs (Buchholz, Paul & Shi, 2005), and they are essential for development in birds (McNabb, 2006) and mammals (Zoeller & Rovet, 2004). There is remarkable evolutionary conservation among vertebrates and some invertebrates in the chemistry of thyroid hormones, as well as in their role in development and adult physiology (Heyland, Reitzel & Hodin, 2004; Heyland & Moroz, 2005). Likewise, the molecular signalling pathways (involving thyroid hormone receptors) through which these hormones exert their actions are highly conserved across the vertebrate taxa (Buchholz, Paul & Shi, 2005; Bertrand et al., 2004; Whitfield et al., 1999).

Endocrine disruptors as risk factors in thyroid disease and dysfunction

Given the importance of thyroid hormone in human and wildlife physiology, and the life-long effects of thyroid dysfunction during development, it is reasonable to carefully consider the possibility that environmental chemicals may interfere with the ability of thyroid hormone to perform its functions. There is a very large list of environmental chemicals – mostly human-made – that can cause a reduction in circulating levels of thyroid hormone in experimental animals (Howdeshell, 2002; Brucker-Davis, 1998). Not all of these produce goitre, although they all reduce serum concentrations of thyroid hormone. Moreover, more environmental chemicals are being identified that can interfere directly with the receptor for thyroid hormone (Zoeller, 2010) or with other processes controlling thyroid hormone action (Gilbert et al., 2011; see **Figure 2.9**).

Thyroid hormone dependent mechanisms of nervous system development in animals and humans

Severe thyroid hormone deficiency produces severe brain damage (Chen & Hetzel, 2010) and moderate or even transient insufficiency can cause specific developmental defects in rodents (Auso et al., 2004; Crofton, 2004; Crofton et al., 2000; Goldey et al., 1995; Goodman and Gilbert, 2007), and in humans (Haddow et al., 1999; Kooistra et al., 2006; Oerbeck et al., 2003; 2007; Pop et al., 1995; 2003; Pop & Vulsma, 2005). Small differences (~25%) in point estimates of maternal T_4 or TSH during the early fetal period are associated with adverse outcomes in humans (e.g. reduced IQ scores), even though hormone levels are not outside the population reference range (Haddow, Palomaki & Williams, 2002; Morreale de Escobar, Obregon & Escobar del Rey 2000). However, in a hallmark study by Bongers-Schokking et al. (2000), the Mental Development Index of children with congenital hypothyroidism was affected by the age of onset of treatment with thyroid hormone, rather than the specific serum free T_4 concentration after treatment. Thus, the degree of

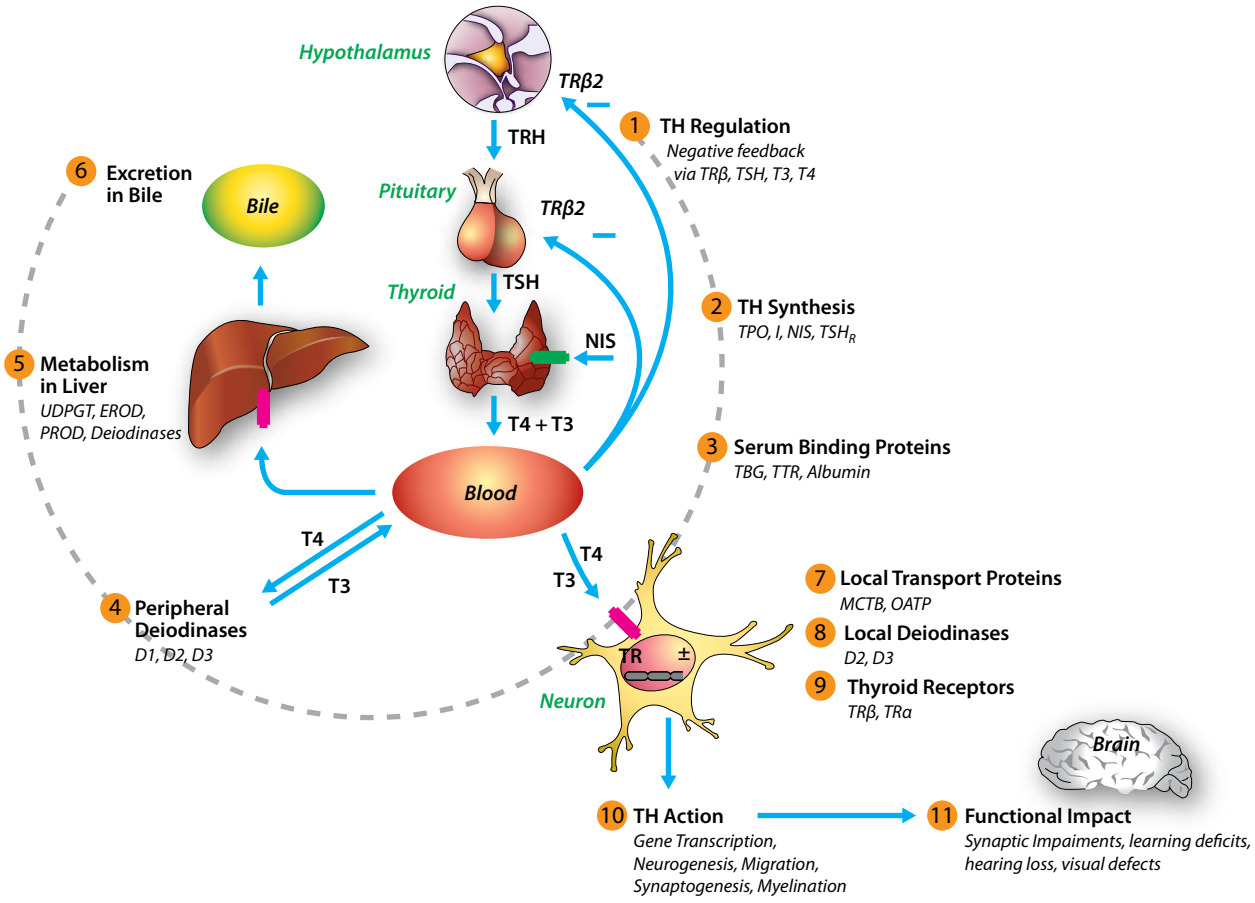

Figure 2.9. Possible sites of action of environmental contaminants on the HPT axis (Figure from Gilbert et al., 2011, redrawn; Used with publisher's permission).

thyroid hormone insufficiency is not the only variable affecting human development; the duration of the insufficiency and the developmental timing of the insufficiency are also important and may vary by species, presenting a challenge for risk assessment. This is discussed further in Chapter 1.2.4)

Experimental work in animals provides strong support for the hypothesis that moderate to mild thyroid hormone insufficiency can alter development in rodents. Integrating data over a series of studies, a decrease in serum total T_4 by 50% during the critical period for cochlear development in the ear was associated with a permanent hearing loss in adult offspring (Crofton, 2004). Moreover, Auso et al. (2004) found that less than a 30% decrease in serum total T_4 in female rodents, for only 3 days, was associated with structural abnormalities in the brains of their offspring. An average decrease in serum total T_4 of only 28% in 2-week-old pups given low doses of propylthiouracil was associated with marked reduction in cell density of the corpus callosum region of the brain (Sharlin et al., 2008). Interestingly, Gilbert & Sui (2008) found that a 28% reduction in circulating levels of T_4 in pregnant rats produced significant adverse effects on synaptic function of hippocampal neurons of their adult offspring despite no detected change in serum T_4 levels in the pups after birth. The US EPA has discovered a cluster of neurons that reproducibly migrates to an incorrect position in the brain of animals that have low thyroid hormone (Goodman & Gilbert 2007). Elements of this cluster very sensitive to prenatal thyroid hormone insufficiency have been characterized (a heterotopia) (Gilbert et al., 2012) . Finally, Sharlin et al., found a very strong inverse relationship between serum T_4 in rat pups and the numbers of myelin-forming oligodendrocytes in major white matter tracks in the brain (Sharlin et al., 2008), and this was not compensated for by elevated serum TSH (Sharlin et al., 2010). Thus, experimental findings confirm what has been observed in humans: small, even transient, decreases in serum total T_4 are associated with altered brain development.

In general, there is strong evidence to conclude that thyroid hormone plays the same general role in brain development of animals and humans (Zoeller & Rovet, 2004). This clearly indicates that rodents represent important test systems to provide information important for protecting public and wildlife health from chemical exposures. In animal studies, the investigator is able to measure the effect of environmental chemicals on blood levels of hormones, and can fully characterize the consequences of these changes on thyroid hormone action at the molecular, cellular and tissue level at various times during development. In addition, a variety of drugs and genetic lines of mice are available to experimentally confirm that environmental chemicals are specifically disrupting thyroid hormone action and not some other pathway of toxicity that could produce similar effects on apical endpoints. In contrast, in human studies, the investigator can only correlate measures of hormone levels in the blood with exposures and with various metrics of health and very few additional measures can be obtained to help interpret the relationship between these variables of interest. Therefore, it is critically important to consider animal studies in the interpretation of human studies.

Notwithstanding this, the current set of validated test methods in the USA and EU for evaluating the ability of chemicals to interfere with thyroid hormone action does not include testing whether the chemical can interfere with thyroid hormone action (Zoeller, Tan & Tyl, 2007a; Zoeller, Tyl & Tan, 2007b).

2.5.2 Evidence for endocrine disruption of the thyroid in humans and in mammalian models of humans

2.5.2.1 Human thyroid diseases and disorders

Thyroid disorders are amongst the most prevalent of medical conditions and include goitres or thyroid nodules (adults), congenital and adult hypothyroidism, autoimmune thyroiditis, hyperthyroidism or Graves' disease and thyroid cancer. In this section, we will deal mostly with congenital and adult hypothyroidism as well as Graves' disease, the remainder being covered in sections 2.11 (autoimmune diseases) and 2.7 (thyroid cancer). As already mentioned, thyroid hormone deficiencies during the development of the brain can also cause neurodevelopmental disturbances leading to mental difficulties, manifest as Attention Deficit Hyperactivity Disorder (ADHD), learning difficulties and possibly even autism. These are discussed further under section 2.6.

Hypothyroidism: This refers to an "underactive" thyroid gland such that it produces too little thyroid hormone. Symptoms associated with hypothyroidism are broad and can be somewhat non-specific including cold intolerance, weight gain, lethargy, and low mentation (Haddow, 2010). Moreover, the body consumes less oxygen and produces less body heat. Hypothyroidism can occur in both children and adults. In the adult population, studies in Northern Europe, Japan and the USA have found the prevalence of hypothyroidism to range between 0.6 and 12 per 1000 women and between 1.3 and 4.0 per 1000 men investigated, although the prevalence is higher in surveys of the elderly (Vanderpump, 2011).

Congenital hypothyroidism: Congenital hypothyroidism (CH) is one of the most common preventable causes of mental retardation caused by thyroid dysgenesis during fetal life. In the first trimester, the fetus is dependent on the trans-placental passage of thyroid hormones of maternal origin because the fetal thyroid gland does not produce thyroid hormone until the end of the first trimester, and then in sufficient quantities only at 20 weeks gestation (Smallridge et al., 2005). Thereafter, however, a hypothyroid fetus will synthesize around 70% less T4 than a normal fetus leading to CH (Olney, Grosse & Vogt, 2010). In 75-80% of all cases of CH, the underlying etiology is unknown, whilst the remaining 15-20% have genetic thyroid dyshormonogenesis. A daily iodine intake <25 µg, particularly in preterm infants, accounts for many cases of CH in Europe, Asia and Africa, but multiple other factors may also be causal elements.

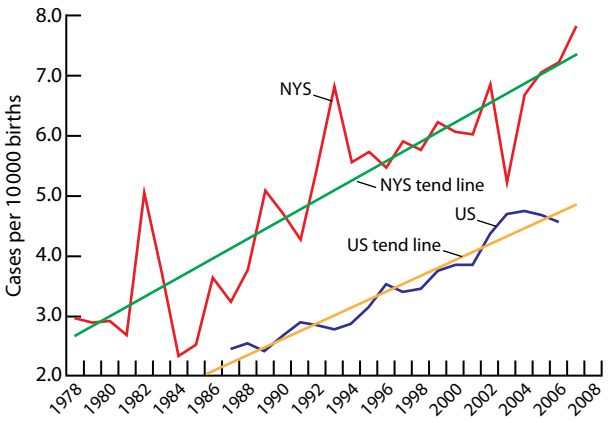

Figure 2.10. Incidence rate of CH in New York State (NYS), 1987–2007, and in the United States (excluding NYS), 1987–2006. (Figure from Hinton et al. (2010), redrawn; Used with publisher's permission).

Estimates of the birth prevalence of congenital hypothyroidism (CH) varies considerably throughout the world where universal screening programs are in place, as reviewed by Rendon-Macias et al. (2008). These estimates range from 1:1403 in Iran to 1:6450 in Latvia.

It was recently reported that the incidence of congenital hypothyroidism has nearly doubled over the past two decades in several countries in which it has been studied including the USA (Harris and Pass 2007; **Figure 2.10**), Western Australia (Kurinczuk et al., 2002), Italy (Corbetta. et al., 2009), the northern UK (Pearce et al., 2010b), and Greece (Mengreli et al., 2010). Some authors speculate that this is due to changes in the cut-off values for the neonatal screening system in the definition of this disorder (Mitchell, Hso & Sahai, 2011; LaFranchi, 2011). This will be an important issue to address.

Subclinical hypothyroidism (mild thyroid failure)

More widespread testing of thyroid function in the absence of suggestive clinical features suggests there are a great number of individuals, not diagnosed with thyroid problems, in which only TSH is abnormal (see **Figure 2.11**). A population study in Colorado, of over 25, 000 individuals of mean age 56 years, showed TSH excess in 9.5 % of the population and suppressed TSH in 2.2%; over half the group with suppressed TSH were taking thyroid medication. Similarly, in the Whickham survey in North East England, 8% of women and 3% of men had subclinical hypothyroidism and in the National Health and Nutrition Examination Survey (NHANES III), approximately 2% of adolescents aged 12–19 years had a serum TSH >4.5 mIU/L.

Prevalence data from one region do not necessarily apply to other populations, because of differences such as ethnic predisposition or variations in iodine intake. Several European studies have compared the effect of various levels of iodine intake on the prevalence of thyroid over- and under-function. Hypothyroidism is generally more common with abundant iodine intake, while goitre and subclinical hyperthyroidism are more common with low iodine intake.

2.5.2.2 Evidence for EDC exposures causing thyroid diseases and disorders.

It is possible that specific chemical exposures could lead to clinical thyroid disease and that this could be reflected in observed secular increases in the incidence or prevalence of thyroid disease. As reviewed above, thyroid disease is defined in large part by the presence of blood levels of T_4 and TSH that are outside the population reference range. For example, clinical hypothyroidism is defined as low T_4 and high TSH; both hormones need to be outside the reference range. However, the clinical symptoms associated with this hormone profile are highly variable in the population, and

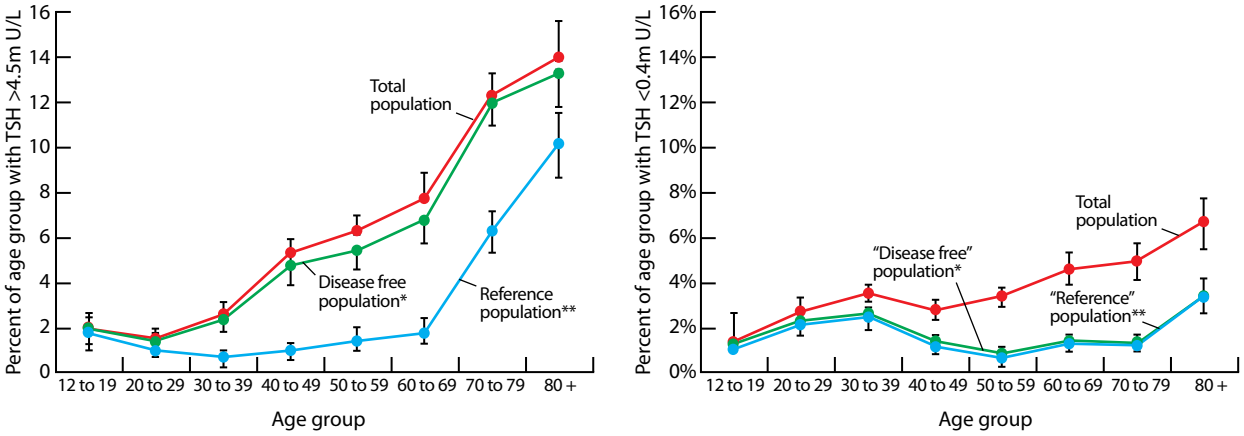

Figure 2.11. Percentage of the USA population (in 2002) with abnormal serum TSH concentrations as a function of age. The disease-free population excludes those who reported thyroid disease, goiter or thyroid-related medications; the reference population excluded, in addition, those who had positive thyroid autoantibodies, or were taking medications that can influence thyroid function. Note the much higher prevalence of TSH abnormalities in the total population, than in the reference population (Figure from Hollowell et al. (2002), redrawn; Used with publisher's permission).

as a result, a significant proportion of the general population can have undiagnosed thyroid disease. In fact, in addition to the 14 million adults in the USA with diagnosed thyroid disease, a further 13 million are estimated to be undiagnosed (Blackwell, 2004). With such a large proportion of likely undiagnosed disease, it is clear that reported changes in incidence or prevalence would not be meaningful. Moreover, because thyroid hormone levels are variable within individuals (Andersen et al., 2003; Andersen et al., 2002), it will be difficult to identify relationships between clinical disease and chemical exposures; in contrast, it may be more likely that chemical exposures will be related to thyroid hormone levels within the reference range. Risk assessors should not disregard such relationships for several reasons:

- First, a large number of chemicals can affect circulating levels of thyroid hormone in animals (Howdeshell, 2002; Brucker-Davis, 1998). Although there are differences between rodents and humans in some characteristics of the thyroid system (see below), rodent systems still provide important fundamental information for the pharmaceutical development of therapeutics for humans. Therefore, it seems inefficient to employ rodent systems to develop drugs but to fail to use rodent systems to protect public health.
- Second, serum TSH levels within the reference range have been identified as a risk factor for blood pressure and serum cholesterol (reviewed in Miller et al., 2009) as well as for bone in postmenopausal women (Morris, 2007). This suggests that serum thyroid hormone levels – TSH and possibly total or free T_4 – will be useful measures to link chemical exposures to various diseases.
- Finally, small differences in serum thyroid hormone levels during pregnancy or at birth are associated with deficits in cognitive function (LaFranchi, 2010). Therefore, if the fetus or neonate is as sensitive to chemical exposures as are adults, then even weak relationships between chemical exposure and hormone levels could produce permanent adverse effects.

A comprehensive review of this literature has recently appeared (Boas, Feldt-Rasmusssen & Main, 2011; Boas, Main & Feldt-Rasmusssen, 2009). There is now reasonably firm evidence that PCBs have thyroid-disrupting effects and that several other common contaminants also have such properties. These include brominated flame retardants, phthalates, bisphenol A and perfluorinated chemicals. In all cases, chemical exposure has been associated with serum thyroid hormone levels. Chemicals may affect circulating levels of thyroid hormone by interacting with the thyroid system in different ways (**Figure 2.9**) and there is currently little information about exactly how these may interact. A key issue is the extent to which changes in circulating levels of thyroid hormone reflect changes in thyroid hormone action in tissues (e.g. Zoeller, 2003). Human exposure to these chemicals (listed in Chapter 3, Table 3.1) is comprehensively reviewed in Chapter 3.2.2.

2.5.2.3 Polychlorinated biphenyls (PCBs)

PCBs are a family of biphenyls that have been randomly chlorinated, producing a mixture of chemicals that have as many as 209 different chlorination patterns. Their biological activity is altered by these patterns; in general, chlorination patterns that stabilize the ring structures into a planar conformation have dioxin-like activity (Kafafi et al., 1993; Kafafi et al., 1992) and those whose chlorination pattern stabilizes the ring structures into a non-coplanar conformation have a variety of activities (Lyng, 2007; Zoeller, 2001; Seegal & Shain, Snyder-Keller & Seagal, 1992; Shain, Bush & Seegal, 1991). Although PCB production was banned in the 1970s, PCBs remain common contaminants in the environment and in humans and wildlife both because of their chemical stability and because of the widespread use from heavy industrial applications to home products such as floor finishes and window caulking.

A number of studies have reported associations between PCB exposure and measures of thyroid function in humans that support the hypothesis that PCBs can reduce circulating levels of thyroid hormone (Abdelouahab et al., 2008; Hagmar et al., 2001a; 2001b; Persky et al., 2001; Schell et al., 2008; Turyk, Anderson & Persky, 2007). Some studies indicate that PCB body burdens suppress serum T_4, whilst others indicate serum T_3. In some cases, the findings are in men, in other cases in women. Overall, it is not a uniform picture. In studies of pregnant women, PCB body burden is positively associated with serum TSH (Chevrier et al., 2007; Takser et al., 2005). Studies of newborns also indicate that PCB body burden suppresses thyroid function (Chevrier et al., 2007; Herbstman et al., 2008). However, a number of studies report no associations between PCB body burden and measures of thyroid function (e.g. Dallaire et al., 2009; Dallaire et al., 2008; Longnecker et al., 2000).

There are a very large number of variables that must be considered to identify a relationship of interest between PCB exposures and measures of thyroid function. These include the fact that PCBs have a very long half-life in the human body and that there are many different PCB congeners that could influence thyroid function differently. There are also slightly different congener profiles in different populations. Measures of thyroid function are also variable across the population (serum total and free T_4 and T_3 and TSH) and this is exacerbated when time-of-day (with which thyroid hormone levels vary) is not standardized. Likewise, there are small gender and population differences. In one study of newborns, the birth mode (caesarean versus vaginal delivery) was important in identifying a relationship between serum PCBs and measures of thyroid function (Herbstman et al., 2008).

Evidence for PCB exposures causing thyroid diseases and disorders in rodent models

Considering these issues, it should be expected that not all studies will find exactly the same relationships. The issue is whether observed correlations between PCB body burden and various measures of thyroid function are consistent with an effect on population health that is mediated by effects on

thyroid hormone action. This is where experimental studies in animal models can be revealing. PCB exposures nearly uniformly cause a reduction in serum total and free T_4 (Gauger, Sharlin & Zoeller, 2007a). However, serum TSH is not often reported to be elevated in response to this decrease (Hood and Klaassen). In addition, different PCB congeners appear to be differentially potent at causing serum T_4 reductions (e.g. Giera et al., 2011), although it is not clear why this is observed. In a controlled study comparing the effects of reduced serum T_4 produced by either propylthiouracil (PTU), which blocks thyroid hormone synthesis, or various PCBs, which presumably induce liver microsomes and decreases the serum half-life of T_4, Giera et al. (2011) found very different effects of PCB exposure compared to PTU exposure. Despite the fact that both exposures brought serum total T_4 to the same concentration in blood, the two exposures had very different effects on the expression of known thyroid hormone response genes in the liver. Thus, the effect of PCB exposure on serum thyroid hormone levels cannot be interpreted the same way as the effect of PTU on serum thyroid hormone levels. This conclusion is supported by other studies (Bansal & Zoeller, 2008; Roegge et al., 2006; Bansal et al., 2005).

These findings also indicate that PCBs, or at least some congeners or metabolites, can interact directly with the thyroid hormone receptor. This hypothesis has been supported by a variety of studies. Several hydroxylated PCBs have been shown to displace T_3 from the TR (You et al., 2006; Kitamura et al., 2005), or to increase (Freitas et al., 2011; Gauger et al., 2007) or decrease (Amano et al., 2010; Miyazaki et al., 2008) thyroid hormone receptor activation in expression systems. Likewise in vivo, PCBs produce effects that are consistent with the hypothesis that they can interfere with thyroid hormone action; in a recent study, PCB body burden in killer whales was highly correlated with the expression of the thyroid hormone receptor (Buckman et al., 2011), a known target of thyroid hormone itself.

Taken together, these findings reveal relatively inconsistent relationships between PCB exposure and measures of thyroid function in humans, but very strong evidence in animals and in molecular studies indicating that PCBs can interfere with thyroid hormone action. The complexity of the human data has been interpreted by some to indicate that there is no convincing evidence that PCBs interfere with thyroid function in humans (Kimbrough & Krouskas, 2003). Moreover, these authors suggest that even if the current data indicate that PCBs can interfere with thyroid function in humans, it is not clinically relevant. Importantly, this review did not include aspects of thyroid measurements that would provide insight into the difficulty in observing PCB effects of interest or the kind of statistical analysis that would be required.

All studies of endocrine disruptors in humans will likely have elements of the dataset observed with PCBs. Specifically, environmental chemicals may produce effects on endocrine systems that are either dissimilar to that of overt disease states, or that are inconsistent from one study to the next due to the difficulty in standardizing exposure measures and measures of hormone levels.

2.5.2.4 Other environmental chemicals

Boas, Feldt-Rasmussen and Main (2011) have also reviewed the literature linking a variety of chemical exposures to thyroid function in humans. These include PBDEs, pesticides, perfluorinated chemicals, phthalates, bisphenol A, UV-filters and perchlorate. With the possible exception of perchlorate, none of these chemicals have been as extensively for their relationship to thyroid function as that of PCBs. Human exposure to these chemicals is, however, extensive (Chapter 3.2.2). Suvorov and Takser (2008) suggest that the PCB story can further inform the number of publications (and time) required to generate enough data to make informed decisions about human and wildlife health.

2.5.2.5 The perchlorate controversy

Perchlorate is an oxidant used in a variety of industrial applications, from the production of solid rocket fuels, to explosives used in automobile airbags, fireworks and blasting caps (reviewed in Oxley et al., 2009). Perchlorate is also naturally occurring (Dasgupta et al., 2006), though the relative degree to which environmental contamination is caused by human-made or naturally occurring perchlorate is not clear. Perchlorate is chemically stable when wet and persists for long periods in geological systems and in groundwater. Largely because of disposal practices during the 1960s – 1990s, perchlorate became a common contaminant of groundwater in the United States (Urbansky, 2002).

The best known biological effect of perchlorate is the inhibition of iodide uptake by the sodium/iodide symporter (NIS) (Wolff, 1998), although it has recently been reported that perchlorate also interacts with Pendrin, another iodide transporter (Attanasio et al., 2011). NIS is responsible for transporting iodide into the thyroid gland, which is required for the production of thyroid hormone (Carrasco, 2000). In addition, this protein is expressed in the gut (Nicola et al., 2009; Vayre et al., 1999), lactating breast (Nicola et al., 2009; Dohan et al., 2003; 2007), placenta (Mitchell et al., 2001), and choroid plexus (Carrasco, 2000), all presumably as a delivery mechanism for iodide to the thyroid gland. In this regard, it is important that the expression of NIS in the human fetal thyroid gland is the limiting step in the production of thyroid hormone (Szinnai et al., 2007).

Given the essential role of thyroid hormone in development, it is important to determine whether perchlorate exposure is associated with measures of reduced thyroid function in the human population. Early studies sought to test this by comparing T_4 or TSH levels in blood spots taken as part of the neonatal screening program with a proxy measure of perchlorate exposure – i.e. the city in which the infant was born (Las Vegas compared to Reno, Nevada, USA) (Li et al., 2000a; 2000b; Crump et al., 2000; Lamm and Doemland, 1999). The hypothesis was that because municipal drinking water was contaminated with perchlorate in Las Vegas but not in Reno, pregnant women and neonates would be exposed to perchlorate in Las Vegas but not in Reno. These studies uniformly found no association between the city of birth and neonatal thyroid

hormone. This was further supported by studies in Chile, in which perchlorate of natural origin is high, and again found no association between neonatal measures of thyroid function and the city of birth (Crump et al., 2000; Tellez Tellez, 2005). It was later shown in national biomonitoring data that almost everyone in the USA is exposed to perchlorate on a continual basis (Blount et al., 2006a; 2006b) and that much of this is derived from food (Huber et al., 2010; Sanchez et al., 2009). Therefore, studies using point estimates of exposure (i.e. city of birth) were confounded by large misclassifications of exposure and provide little useful information concerning the relationship of interest, i.e. perchlorate exposure and thyroid function.

A separate series of studies were performed to determine the efficacy of perchlorate exposure on iodide uptake inhibition in human volunteers (Greer et al., 2002; Lawrence, Lamm & Braverman, 2000; 2001), with the idea that this would help determine whether human exposures could influence thyroid function in the general population. These studies indicated that adults would have to consume 2L of drinking water daily that was contaminated with at least 200 ppb (µg/L) perchlorate to reach a level in which iodide uptake would begin to be inhibited (Greer et al., 2002). Of course, the relationship between iodide uptake inhibition, thyroid hormone synthesis and serum concentrations of thyroid hormone is not known, but was believed to require significant iodide uptake inhibition for extended periods before thyroid function would be impaired. Based on these studies, a USA National Academy of Science (NAS) committee recommended a reference dose (RfD) of 0.0007 mg/kg per day (National Research Council, 2005), which the US EPA used to set a provisional drinking water standard of 15 ppb.

Several authors disagreed with EPA's drinking water standard of 15 ppb and perchlorate remediation goal of 24.5 ppb on the basis that it did not consider infants (Ginsberg et al., 2007). The reason for this was that infants must synthesise their supply of thyroid hormone each day (van den Hove et al., 1999); thus, if environmental factors reduce thyroid hormone synthesis and hormone levels decline, adverse effects on cognitive function would develop. Infants are very sensitive to thyroid hormone insufficiency (Zoeller & Rovet, 2004) and small differences in circulating levels of thyroid hormone in infants have been associated with differences in measures of cognitive function into adulthood (LaFranchi & Austin, 2007; Oerbeck et al., 2003; Heyerdahl & Oerbeck, 2003). Ginsberg et al. (2007) calculated that as many as 90% of nursing infants may exceed the RfD, although later empirical measurements indicate that this number is probably closer to 10% (Valentin-Blasini et al., 2011).

Blount et al. (2006b) showed a significant and sizable association between urinary perchlorate and serum thyroid hormones in a statistically representative sample of the USA population as part of the NHANES survey. This association was observed for women, but not for men. Importantly, the associations observed are plausibly consistent with a cause-effect relationship. That is, urinary perchlorate was positively associated with serum TSH and this association was stronger when urinary iodide was low. In addition, urinary perchlorate was negatively associated with serum T_4 levels when urinary iodide was low. Thirty percent of women in this study had low urinary iodide (below 100 µg/L). Using this same dataset, Steinmaus, Miller & Howd, (2007) showed that women who smoked had elevated levels of thiocyanate, which also inhibits iodide uptake by the NIS, and that in women with low urinary iodide, the association between perchlorate exposure and measures of thyroid function was much stronger.

Conclusions from the NHANES 2001-2002 data are not easily reconciled with the earlier studies of human volunteers or with other population studies (Pearce et al., 2010a; 2011). If these studies reflect a true relationship between very low levels of perchlorate exposure and thyroid function, it would mean that data derived from short-term, high-dose experiments in humans do not accurately predict effects of chronic low-dose exposures.

The conflicting findings among epidemiological studies of the relationship between perchlorate exposure and thyroid function should highlight features of the thyroid system that do not appear to be commonly taken into consideration. One of the most important of these is that circulating levels of thyroid hormone are somewhat variable in each individual (Andersen et al., 2002). In fact, Andersen et al. (2002) estimate that it would require 25 separate tests to estimate the "set point" for serum T_4 in a single individual with a precision of 5%. Thus, the known variability in measurements of T_4 and TSH should be employed to estimate the number of subjects needed to test whether there is a relationship between serum T_4 and perchlorate. Likewise, consideration needs to be given to the known variability of estimates of perchlorate exposure. None of the current studies formally calculate the number of participants that would be required to identify a relationship between serum T_4 (or TSH) and urinary perchlorate. The Blount study included over 1,111 women in their study – the largest to date.

The story of perchlorate contamination should be used to inform studies of other contaminants and their relationship with thyroid function. For those exposures that will act by changing circulating levels of thyroid hormone, perchlorate can serve as a direct example and it will be important to ensure that the study has enough subjects to provide adequate statistical power. This is important because there are known associations between circulating levels of thyroid hormone in pregnant women and, especially, neonates that provide very strong evidence linking hormone levels to adverse outcome. However, for exposures to chemicals that can interfere with thyroid hormone signalling without affecting serum hormone levels, there is clearly a lack of approach at this moment to test these associations in the human population.

2.5.3 Thyroid hormone and other organ systems

It is important to recognize that thyroid hormone concentrations are correlated with adverse effects in organ systems other than the nervous system in the adult, including the cardiovascular system and control of serum lipids (Asvold et al., 2007a; Biondi et al., 2005; Osman et al., 2002), pulmonary system (Krude et al., 2002; Lei et al., 2003; Mendelson & Boggaram, 1991) and

kidney. Total cholesterol, low density lipoproteins (LDL), non-high density lipoproteins (non-HDL), and triglycerides increase linearly with increasing TSH, and HDL decreases consistently with increasing TSH across normal reference ranges without evidence of any threshold effect (Asvold et al., 2007b). Similar trends in lipid profiles can be identified across clinical categories from hypothyroid to euthyroid to hyperthyroid individuals (Canaris et al., 2000). Within the reference ranges for TSH, there is a linear positive association between TSH and both systolic and diastolic blood pressure (Asvold et al., 2007b). Intimal medial thickness (IMT), a measure of atherosclerosis and predictive of coronary vascular disease and stroke, is inversely related to free T_4 after controlling for lipids, clinical factors, and thyroid autoantibodies (Dullart et al., 2007). Some of these measures are ameliorated by treatment with thyroxine. Not surprisingly, deficits in thyroid homeostasis are associated with cardiovascular risk in multiple epidemiologic studies. A meta-analysis of 14 epidemiologic studies (Rodondi et al., 2006) found an overall increase in risk of coronary heart disease (CHD) of over 65% in those with subclinical hypothyroidism (elevation in TSH with normal T_4). A higher risk was noted in those studies that adjusted for most cardiovascular risk factors. Treatment with L-thyroxine of patients with subclinical hypothyroidism resulted in improvements in cardiovascular risk factors including total cholesterol and endothelial function (Razvi et al., 2007). In addition, environmental exposure to at least one thyroid disrupting chemical (PCBs) has been shown to have an inverse association with T_3 in men (Meeker, Altshu & Hauser, 2007) and was associated with both unfavorable lipid profiles and self reported cardiovascular disease in men and women (Goncharov et al., 2008). Therefore, epidemiologic as well as mechanistic and therapeutic evidence substantiates the concern that thyroid disrupting chemicals may adversely affect cardiovascular risk in humans by reducing serum T_4.

2.5.4 Evidence for endocrine disruption of the thyroid in vertebrate wildlife

Thyroid hormone is produced in all vertebrate classes and the chemistry of the hormone is identical in all of these species. In addition, thyroid hormones play a role in development in at least some members of all vertebrate classes. For example, in the flounder, metamorphosis is thyroid hormone dependent. This is also the case for amphibians. Much less is known about the capacity for thyroid dysfunction by EDCs in reptiles and in birds (with the exception of chick development, which provides an important developmental model). Thyroid hormone receptors (both TRα and TRβ) are highly conserved among the vertebrates, suggesting that thyroid disruptors in any vertebrate may exert similar effects across all vertebrate species. However, metabolism of chemicals and subsequent exposures may differ considerably among the vertebrates and there may be other important differences that would suggest that caution be used when extrapolating information from one vertebrate class to another.

Thyroid hormone disruption reported in vertebrate wildlife species includes cetaceans and other sea mammals, as well as a range of fish and birds. Some examples are given in the following sections. Effects on invertebrate wildlife have not been included: whilst thyroid hormone receptor orthologues have been reported across a range of invertebrate species, including the platyhelminths, *Schistosoma japonium* and *Schmidtea mediterranea*, the mollusc, *Lottia gigantea,* and the arthropod, *Daphnia pulex* (Wu, Niels & LoVerde, 2007), the capacity for thyrotoxic chemicals to exert effects on invertebrates is, as yet, unknown. Exposures of wildlife to thyroid hormone disrupting chemicals are comprehensively reviewed in Chapter 3.2.1.

2.5.4.1 Wild mammals

Many studies have reported relationships between individual body burdens of persistent organic pollutants and thyroid-related effects in seals (Brouwer, 1989; Hall, Kalantzi & Thomas, 2003; 2007; Routti et al., 2008), sea lions (Debier et al., 2005), beluga whales inhabiting the St. Lawrence estuary (DeGuise et al., 1995), the harbour porpoise (Schnitzler et al., 2008), and the polar bear (Braathan et al., 2004, Skaare et al., 2001), suggesting contaminant-mediated disruption of thyroid homeostasis. In some studies, interfollicular fibrosis could be seen in the thyroid gland itself, associated with severe pathological dysfunction in other animals. PDBEs and PCBs particularly affect thyroid hormone transport and metabolism (Hallgren et al., 2001; Zhou et al., 2001; Zhou et al., 2002). Thyroid hormones are described as having a permissive role in the effects of other hormones and various enzymes, are important for metabolic regulation and are necessary for adequate growth. They control some aspects of fasting and may play a role in moulting cycles (Bentley et al., 1998). They are therefore key components of the endocrine system of wild mammals and any effects on their production, secretion, metabolism and target sites will have consequences for a range of physiological processes.

2.5.4.2 Non-mammalian vertebrates

Fish in contaminated locations are known to have impaired thyroid systems. The most famous historical examples of thyroid disruption were in the salmonids living in heavily polluted regions of the Great Lakes area in the United States during the 1970s and 1980s (e.g. Leatherland & Sontesgard, 1980a; 1980b; 1982a; 1982b; reviewed in Jobling & Tyler, 2003). Moreover, in the last decade, thyroid abnormalities were also reported in mummichogs from a polluted site in New Jersey, USA (Zhou et al., 2000) and in San Francisco Bay, California, USA (Brar et al., 2010). In the latter study, plasma concentrations of T_4 were significantly reduced in two species of fish from highly contaminated areas, compared with fish from cleaner locations in the same estuary and both the T_3:T_4 ratio and T_3 concentrations were positively correlated with PCB concentrations measured in the livers of the exposed fish whilst T_4 concentrations were inversely correlated. Taken together, the results support the conclusions from laboratory experiments and the general hypothesis already indicated in some marine and terrestrial mammals that environmental PCBs may alter T_4 deiodination or turnover. Relationships between exposure to other chemicals

and thyroid hormone disruption in fish are less common, albeit increasing in the last decade, especially in relation to exposure to flame retardants (PBDEs).

In birds, biomarkers of exposure to thyroid-disrupting chemicals have also been evaluated by McNabb (2005), Panzica, Viglietti, Panzica & Ottinger (2005), and Grote et al. (2006). However, the exact extent to which EDCs exert effects on bird populations is still not established and field studies do not always support extrapolation from laboratory studies (e.g. Fernie et al., 2003; Fernie, Bortolotti & Smiths, 2003a; Fernie, Smiths & Bortolotti, 2003b), possibly because of between-species differences in susceptibility. Notwithstanding this, the relationships between the PCB concentrations and thyroid dysfunction in various bird species conducted over a long period strongly suggest that some PCBs can modulate this system in wild birds. This suggestion is now also supported by results from experimental studies on various model species. Long-term monitoring of herring gulls in the Great Lakes revealed significant thyroid dysfunction linked with PCB burden (Scanes & McNabb, 2003), and structural thyroid abnormalities detected in great cormorants from Tokyo Bay were also associated with PCDF and PCB contamination (Saita et al., 2004).

In addition, other studies on birds have found negative correlations between blood T_4 and T_4:T_3 ratio and levels of organochlorines, particularly hexachlorobenzene and oxychlordane, in glaucous gulls from the Barents Sea (Verreault et al., 2004). Similarly, reduced T_4 levels were reported in white stork nestlings exposed to pollution from a copper smelter (Kulczykowska et al., 2007). In contrast, an increase in T_3 and T_4 levels were detected within the thyroid glands of tree swallow nestlings from reclaimed wetlands partly filled with mine tailings from oil sands processing in Alberta, Canada (Gentes et al., 2007). It was postulated that the modulation of thyroid function in these birds may adversely affect metabolism, behaviour, feather development and moulting, ultimately compromising the survival of fledglings. High body burdens of PCBs in the European shag were associated with increased fluctuating wing asymmetry and also with disruption of the thyroid hormone, vitamin A (retinol) and vitamin E (tocopherol) homeostasis (Jenssen et al., 2010). Intergenerational effects of PCB exposure have also been demonstrated in kestrels, primarily via maternal transfer but also attributable to behavioural effects in the male parent. Where one or both parents had been exposed in ovo to PCBs, the progeny exhibited effects on development and growth, and sexually dimorphic effects on plasma T_3 levels (Fernie et al., 2003b).

2.5.5 Evidence for a common EDC mechanism of thyroid disruption for human and wildlife

From the above, it is apparent that many of the symptoms associated with thyroid hormone disorders in humans, namely alterations in the levels of circulating thyroid hormones and changes in the structure of the thyroid gland, have also been reported in wildlife. However, although probable, as yet there is no evidence that directly links the disruption of thyroid function via chemical exposure to adverse ecological effects in any wildlife species. In contrast, evidence of adverse effects is beginning to emerge from laboratory-based studies and will be discussed in the following section.

2.5.5.1 Evidence for EDC causation of thyroid disruption in laboratory studies with rodents and other vertebrates

Much of the laboratory-based research into the implications of EDC exposure for thyroid function in humans stems from studies using rodent models. For example, the rat has been extensively used to explore the health effects of exposure to PBDEs, with most studies consistently reporting a negative correlation with T_4 concentrations (Zhou et al., 2002; Kodavanti & Derr-Yellin, 2002; Darnerud et al., 2007). Indeed, Kuriyama et al. (2007) demonstrated that BDE-99 has the capacity to reduce T_4 levels in rats, even at low and environmentally relevant doses, with adipose tissue concentrations of BDE-99 in rats close to those reported in non-occupationally exposed humans and also at equivalent doses to those associated with other adverse outcomes in male and female rats, including permanent changes in neurobehaviour, locomotor activity and fertility (Kuriyama et al., 2005). Thus, it would appear that, in rodents, effects on thyroid function occur at EDC concentrations close to current human body burdens.

There is also laboratory-based evidence to support the assertion that EDCs are involved in the causation of thyroid disorders in wildlife species. For example, the suggestion that organochlorine pesticides, PCBs and flame retardants are causing thyroid disruption in arctic wildlife is supported by data from experimental studies on various model species such as domesticated arctic foxes, Greenland sled dogs and goats (e.g. Lyche et al., 2004; Oskam et al., 2004; Ropstad et al., 2006 Sonne et al., 2009). As a model of high trophic level carnivores, Kirkegaard et al. (2011) exposed female Greenland sled dogs and their pups to whale blubber contaminated with organohalogen compounds from 2-18 months of age and then examined thyroid hormone status. Although the sample numbers were low, the results supported observational data in other wildlife and humans, by showing that long term exposure to EDCs may result in detectable effects on thyroid hormone dynamics by lowering both free and total T_3.

In non-mammalian vertebrates, there are many laboratory studies reporting the effects of EDCs on thyroid hormone homeostasis, particularly in amphibians, due to the role of thyroid hormone in inducing metamorphosis. In this respect, BPA has been shown to block thyroid hormone-induced metamorphosis, indicating anti-thyroid activity (Iwamuro et al., 2003), which is consistent with its antagonism of T_3 binding in *Xenopus* tadpoles (Goto et al., 2006). The herbicide acetochlor was also found to accelerate T_3-induced metamorphosis of *Xenopus* (Crump et al., 2002), a process that was preceded by disruption of T_3-

dependent expression of thyroid hormone receptor genes in the tadpole tail. Nonylphenol had an overall inhibitory effect on the rate of bullfrog tadpole metamorphosis (Christensen et al., 2005). Gutleb et al. (2007) developed a synchronized amphibian metamorphosis assay, which is based on a the analysis of a range of endpoints, including the percentage of metamorphosed froglets by the end of the 60-day experimental period and the percentage of tadpoles at different stages of development, using *Xenopus laevis* as a model. Using this assay as a tool, a range of thyroid hormone disturbances were observed in response to a mixture of PCBs.

Although differences in sensitivity have been reported, depending on the model in question, in general, it would appear that the same chemicals, or groups of chemicals, elicit similar response patterns regardless of the species in question and the test system used. Laboratory-based studies using mammalian (mainly rodents) and non-mammalian species (most notably amphibians) have been invaluable in demonstrating the capacity for EDCs to affect thyroid development and in helping to identify critical periods of exposure during development. The data generated by these studies support the theory concerning the involvement of EDCs in the causation of thyroid disorders in wildlife and, in many cases, mirror the evidence concerning the etiology of these disorders in humans.

2.5.5.2 Interspecies extrapolation

Interspecies extrapolation of adverse effects of EDCs requires careful consideration. An example in which cross-species extrapolation is warranted is that of perchlorate. Perchlorate competitively inhibits iodine uptake into the thyroid gland, with subsequent decreases in TH synthesis and declines in circulating TH concentrations (Wolff, 1998). The kinetics for perchlorate inhibition of iodine uptake in humans and rats are extremely similar (US EPA, 2002), indicating the homologous nature of the initial toxic event. Although this is a clear example of a situation in which the toxic event (i.e. iodine uptake into the thyroid gland) exhibits similar kinetic profiles for rodents and humans, the impact of reduced serum thyroid hormone in rodents and humans may differ in some characteristics. For example, rodents or humans may possess robust compensatory mechanisms that would ameliorate the impacts of perchlorate exposure or low T_4 (National Research Council, 2005). However, it is not at all clear that this is the case. Studies in humans indicate that even mild iodine insufficiency is associated with lower IQ in children (Berbel et al., 2009; Zimmermann, 2007; Aghini Lombardi et al., 1995), which does not support the notion that compensatory mechanisms are robust or available to the developing brain. Moreover in animals, Gilbert & Sui (2008) found that perchlorate exposure of pregnant rats can significantly affect synaptic transmission in the adult offspring, which also indicates that robust compensatory mechanisms to low thyroid hormone are not available. In addition, Sharlin et al. (2010) failed to identify compensatory responses to low levels of thyroid hormone in the developing rodent brain.

In contrast to the above, some studies do not support direct extrapolation between species (Crofton, 2004). To illustrate this kind of situation, both in vivo and in vitro studies suggest that PCBs activate the pregnane X receptor (PXR) in rodent liver, which leads to upregulation of hepatic catabolic enzymes and subsequent declines in circulating concentrations of T_4 (Schuetz, Brimer & Schuetz, 1998). The steroid X receptor (SXR) is the human equivalent of rodent PXR (Blumberg et al., 1998) and there are species differences between these two proteins. Rodent PXR is activated by pregnenolone-16α-carbonitrile (PCN), but not by rifampicin, whereas human SXR is activated by rifampicin but not by PCN (Kliewer, Goodwin & Willson, 2002). In addition, in vitro data suggest that high concentrations of CB-153 act as an antagonist at the human SXR rather than an agonist on the PXR in rodents (Tabb et al., 2004). Thus, PCBs may cause serum T_4 to decline in animals but not in humans. While these data appear to support the conclusion that rodent data for PCBs are not relevant to humans, it does not appear to be that simple. First, if the hypothesis is correct that PCB, increase T_4 clearance in a manner similar to that of phenobarbital, then serum TSH should increase as it does in response to phenobarbital (Hood & Klaassen, 2000). Because TSH does not increase in response to PCB exposure in rodents, the mechanism(s) by which PCBs cause a reduction in serum T_4 may not be well understood. In addition, we know that some PCB congeners or metabolites can interact directly with the TR (see above), which is not related to a PXR/SXR pathway. Thus the mechanisms by which PCBs cause a reduction in serum T_4 even in animals are not fully understood, nor have the most important pathways of toxicity in animals or humans been identified. Thus, the information required to exclude animal studies for consideration in risk assessment for PCBs is not available. Moreover, there are few other chemicals for which so much information is available. Therefore, it is unlikely to be the case that animal-to-human extrapolation should be excluded.

Finally, some authors propose that there are differences in circulatory transport proteins for thyroid hormones (e.g. transthyretin and thyroid-binding globulin) in rodents compared to humans and that this renders rodents much more sensitive to thyroid hormone reducing agents than are humans (Capen, 1997; Hill et al., 1998). However, it is not clear that these differences are meaningful for two reasons. First, pregnant and neonatal rodents have high levels of all transport proteins including thyroxine binding globulin (TBG) (Savu et al., 1991; Vranckx, Savu & Nunez, 1989; Savu et al., 1989; 1987). Rat TBG has been cloned (Tani et al., 1994) and its regulation studied (Vranckx et al., 1994). Thus, the contention that rodents do not have the same serum binding proteins as humans may not be correct. A further difference between rodents and humans is that the serum half-life of T_4 in rodents is much shorter than that of humans (1 day in rodents versus 7-10 days in humans), although it is not at all clear that this issue renders rodent studies of thyroid function irrelevant to humans either; there are considerable data that suggest just the opposite.

2.5.6 Main messages

- Thyroid hormone is important in development and in adulthood in both wildlife and humans.
- Aside from thyroid cancer and congenital hypothyroidism, it is difficult to identify trends in the incidence of human thyroid disease.
- There are many chemicals that can interfere with thyroid function.
- Similarly, there are chemicals that can interfere directly with thyroid hormone action.
- Many chemicals interfere with thyroid function in a manner that will not be captured by evaluating only serum hormone levels.
- Despite the recognition that thyroid hormone is essential for brain development in humans, few if any chemicals are tested for their ability to interfere with thyroid hormone action.
- Relationships between exposure to chemicals and thyroid hormone disruption in wildlife species have increased in the last decade, especially in relation to exposure to flame retardants (PBDEs) and PCBs.
- The strength of evidence supporting a role for endocrine disrupting chemicals in disrupting thyroid function in wildlife adds credence to hypothesis that this could also occur in humans.
- Thyroid disruption is acknowledged to be poorly addressed by the chemical tests currently listed in the OECD Conceptual Framework.

2.5.7 Scientific progress since 2002

Since the *Global Assessment of the State-of-the-Science of Endocrine Disruptors* (IPCS, 2002), the following advances have been made:

- Increasing numbers of human studies establish a link between chemical exposures and thyroid function, including in pregnant women.
- However, few studies have focused on the relationship between chemical exposures in pregnant women, thyroid measures in those women (or in the cord blood of their offspring), and cognitive function in neonates.
- Genetic lines of mice have become widely available that should be coupled with toxicology studies to help clarify the mechanisms by which chemical exposures can interfere with thyroid hormone action.
- Relationships between exposure to chemicals and thyroid hormone disruption in wildlife species have increased in the last decade, especially in relation to exposure to the flame retardants (PBDEs) and PCBs, but other chemicals are insufficently studied.

2.5.8 Strength of evidence

There is sufficient evidence that some thyroid diseases are increasing in the human population and that this baybe related to environmental exposures. These diseases include congenital hypothyroidism and thyroid cancer. This evidence is considered to be sufficient because several authors report an increased incidence using screening data that reflect population-wide surveys. However, there are insufficent data linking these increases in thyroid disease to specific environmental factors.

There is limited evidence from wildlife studies and sufficient evidence from laboratory experiments that endocrine disrupting chemicals can interfere with thyroid hormone signalling, leading to diseases and disorders in wildlife species. The data generated by these studies support the theory concerning the involvement of EDCs in the causation of thyroid disorders in wildlife and mirror some of the evidence seen in humans. For many wildlife species, however, no studies have been done.

There is insufficient direct evidence in the human literature supporting the hypothesis that effects on thyroid hormone signalling mediate the association between chemical exposures and human disease/disorders. Perhaps the best example of this is focused on PCBs. There is sufficient evidence linking PCB body burden to reduced measures of cognitive function in children (Schantz, Widholm & Rice, 2003) and this evidence is deemed to be sufficient because a number of authors have reported similar findings and because it is consistent with studies in animals. In animal studies, PCBs clearly reduce circulating levels of thyroid hormone (Brouwer et al., 1998) and can affect brain development (Roegge et al., 2006). There are some studies indicating that PCB body burden is linked to reduced measures of cognitive function, but the evidence demonstrating a causal relationship is limited. Few studies have evaluated the relationship between PCB exposure, cognitive development, and thyroid hormone; therefore, there is overall insufficient evidence to demonstrate that PCBs interfere with thyroid hormone signalling and cause an adverse effect. Animal studies indicate that PCBs can exert effects on thyroid hormone signalling in development that are not consistent with effects on serum hormone levels (Bansal & Zoeller, 2008; Giera et al., 2011). Therefore, while considerable evidence exists in animal studies that chemicals can interfere with thyroid hormone signalling during development and produce adverse outcome, we have not developed the approach to fully test this hypothesis in human populations.

Thus, there are insufficient data linking chemical exposures to altered thyroid hormone signalling and the occurrence of disease or dysfunction in humans. Clearly, considering the importance of thyroid hormone during development, the large knowledge gaps, animal data, and the economic cost of population wide impacts on thyroid function during development (Dosiou et al., 2008), these are issues that need to be addressed quickly.

2.5.9 References

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