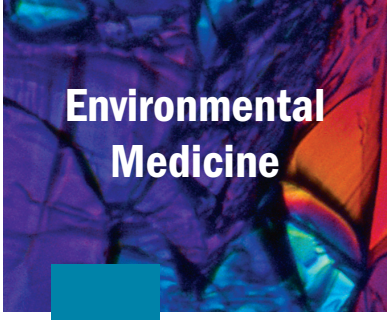

Thyroid Disruption: Mechanisms and Clinical Implications in Human Health

Lyn Patrick, ND

Abstract

Exposure to specific environmental toxins, including polychlorinated biphenyls, dioxins, phthalates, polybrominated diphenyl ethers (PBDEs), and other halogenated organochlorines, has been shown to interfere with the production, transportation, and metabolism of thyroid hormones by a variety of mechanisms. A broad range of chemicals, with structural similarity to thyroid hormone, have been shown to bind to thyroid receptors with both agonist and antagonist effects on thyroid hormone signaling. The incidence of thyroid disease in the United States, particularly for thyroid cancer and thyroid autoimmune disease, is increasing substantially. The evidence for the significant effects of background levels of thyroid-disrupting chemicals, the known pathways for thyroid disruptors, and the evidence and implications for neurodevelopmental damage due to thyroid-disrupting chemicals is reviewed. *(Altern Med Rev* 2009;14(4):326-346)

Introduction

The Endocrine Society, an international group of 14,000 clinicians and researchers in the field of endocrinology, published a scientific statement: "Endocrine-Disrupting Chemicals" in 2009, available online at http://www.endo-society.org/advocacy/policy/index.cfm.[1] The paper listed the known effects of a group of environmental pollutants termed endocrine disruptors and defined them as "compounds natural or synthetic which through environmental or inappropriate developmental exposures alter the hormonal and homeostatic systems that enable the organism to communicate with and respond to its environment." The statement is a response to the large body of evidence accumulated in the last two decades on the relationship between environmental exposure to a specific class of chemicals and its effects on the endocrine and nervous system. Chemicals that affect thyroid metabolism, either through the hypothalamic-pituitary axis or directly via nuclear receptors, are termed "thyroid disruptors" (TD). A review of at least 150 industrial chemicals summarizes the evidence in animal studies that these chemicals can cause a reduction in thyroid-stimulating hormone (TSH) as well as thyroxine.[2] An extensive review by Brucker-Davis cites 381 wildlife and experimental animal and human studies analyzing the effects of specific drugs and chemicals on thyroid metabolism and subsequent neurodevelopmental and endocrine effects in offspring and children.[3]

Evidence linking polychlorinated biphenyls (PCBs) and specific organochlorines to thyroid disruption began to appear when a monitoring program in Canada documented that herring gulls in the Great Lakes area were repeatedly found with serious thyroid abnormalities and other endocrine pathologies. Other research found that every top predator fish examined in the Great Lakes had enlarged thyroid glands. In addition, the thyroid glands of fish in Lake Erie were found to rupture due to severe enlargement.[4]

Although the extensive 1998 review[3] concluded that occupational or accidental exposure to endocrine disruptors was linked to thyroid changes, the evidence at that time did not link background exposure to significant thyroid pathology. However, Brucker-Davis did conclude that the "impact of transgenerational, background exposure *in utero* on fetal development and

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later cognitive function" was a matter of serious concern. In the ensuing decade, research in the area of endocrine disruption has been extensive (The Endocrine Society Scientific Statement cites 485 references), and concern for the effect of endocrine disruption on children, adult, and fetal health is mounting.[5,6]

This review evaluates what is known about the mechanisms by which thyroid-disrupting chemicals affect thyroid metabolism and increase the risk for thyroid disease, and how those effects may manifest *in utero*, in children, and in adults. And lastly, given the current levels of background exposure to environmental endocrine disruptors that all humans face, the article outlines possible courses of action for health care practitioners.

Thyroid Disease: The Size of the Problem

The National Health and Nutrition Examination Survey (NHANES) is conducted by the Centers for Disease Control and Prevention every two years to establish epidemiological data, nutritional evaluation, and biomonitoring for chemical exposure for a representative U.S. population. In the database of NHANES III (17,353 adults), it was estimated that 20 million people in the United States have either clinical or subclinical (mild) hypothyroidism or hyperthyroidism; approximately 7.5 percent of the U.S. population at the time of the 1994 survey.[7] Hypothyroidism was defined as clinically significant with TSH >4.5 mU/L and thyroxine (T4) <4.5 mcg/dL; subclinical or mild was defined as a TSH >4.5 mU/L and T4 >4.5 mcg/dL. Hyperthyroidism was defined as clinically significant with a TSH <0.1 mU/L and T4 >13.2 mcg/dL; subclinical or mild was defined as TSH <0.1mU/L and T4 <13.2 mcg/dL. In comparison, the incidence of adult-onset type 2 diabetes in the same NHANES population was eight percent.[8] In the NHANES thyroid data the number of individuals in the study who reported diagnosed thyroid disease represented 10.4 million in the U.S. population and the remaining 8.7 million equivalent did not report thyroid disease even though lab values qualified them as being either mildly (subclinical) or clinically hypo- or hyperthyroid.

Another large study of 25,862 people attending a state-wide health fair in Colorado found that 9.5 percent had TSH values >5.01 mU/L and 2.2 percent had TSH <0.3 mU/L, a higher number than the NHANES report. Only 60 percent of people taking thyroid medication had what were considered normal (>0.3 and <5.01 mU/L) serum TSH values.[9]

An ongoing discussion in the endocrinology community suggests lowering the upper limit of the TSH reference range to 2.5-3.0 mU/L.[10] In recently published guidelines, the National Academy of Clinical Biochemistry reports that: "In the future, it is likely that the upper limit of the serum TSH euthyroid reference range will be reduced to 2.5 mU/L because 95 percent of rigorously screened normal euthyroid volunteers have serum TSH values between 0.4 and 2.5 mU/L."[11] The American Academy of Clinical Endocrinology, in their 2002 Guidelines, suggested that the target TSH level for thyroxine replacement should be between 0.3 and 3.0 mU/L.[12] New guidelines for a TSH reference range of 0.3-3.0 mU/L would double the number of people with abnormal thyroid function, bringing the total to as much as 20 percent of the adult population, up from 4.6 percent thought to be hypothyroid under the old guidelines.[13]

Ten percent of 20- to 29-year-old participants in NHANES III (1988-1994) had a serum TSH level over 2.5 mU/L. In the 40- to 49-year-old category, 20 percent had a TSH over 2.5 mU/L. In the eldest category: 80+ years of age, 36 percent had a TSH over 2.5 mU/L.[14] When those in the NHANES study with thyroid antibodies were excluded, the reference range of those remaining with no evidence of thyroid disease had an upper limit of approximately 3.5 mU/L.[15]

There is a continuing debate about the accuracy and appropriateness of diagnosing and treating those with a TSH below the current reference range of 4.0-5.0. If the 2.5-3.0 mU/L level is applied, 22-28 million additional individuals in the United States would be considered hypothyroid. In the studies that follow, unless stated otherwise, the diagnosis of subclinical hypothyroidism generally refers to serum TSH levels between 4.0-4.5 and 10.0 mU/L. Currently the U.S. Environmental Protection Agency defers to the American Academy of Clinical Endocrinology in stating that free T4 and highly sensitive TSH are the appropriate laboratory markers for evaluating thyroid health, although some studies discussed below only found thyroid disruptor effects on tri-iodothyronine (T3) (free and total).[12]

Thyroid Autoimmune Disease

Thyroid autoimmune disease (TAD) is part of a growing phenomenon of the epidemic of autoimmunity. Autoimmune diseases are now diagnosed in more than 24 million people in the United States, compared to cancer in 9 million and cardiovascular disease in 22 million people. Because only one-third of those with autoimmune diseases are believed to be diagnosed, the true statistic is estimated to be three times higher – as high as 72 million.[16] TAD is the most common autoimmune disease, affecting 7-8 percent of the population (10 percent of women and three percent of men) totaling 24 million people.[17,18] TAD is actually a cluster of diseases that include Hashimoto's thyroiditis, idiopathic myxedema, asymptomatic thyroiditis, endocrine exophthalmos, and Graves' disease.[19]

TAD is a complex autoimmune phenomenon; at least half of those with a TAD diagnosis have other antibodies and possibly other autoimmune syndromes. In a recent study, 53 percent of TAD patients in an endocrinology clinic also had other concomitant autoimmune diagnoses or the presence of antibodies found commonly in other autoimmune diseases, including type 1 diabetes, pernicious anemia, chronic atrophic gastritis, vitiligo, alopecia, myasthenia gravis, celiac disease, autoimmune hemolytic anemia, multiple sclerosis, lupus, or Sjogren's syndrome.[20] This phenomenon of multiple antibody generation is hypothesized to be a result of environmental exposure to chemicals that alter immune function through a variety of mechanisms, including genetic modification, a known function of thyroid disrupting chemicals.[21]

Although the evidence is becoming clearer that TAD is complex, most research on endocrine disruptors and thyroid metabolism has only focused on measuring TSH, T4, and the presence of the most common thyroid antibodies: thyroperoxidase antibodies (TPOAb) and thyroglobulin antibodies (TgAb). Results from NHANES III research indicates that 13.0 percent of the total U.S. population is positive for TPOAb and TgAb.[15] Other data from NHANES III also indicated that a positive TPOAb was strongly associated with a diagnosis of either subclinical or clinical hypo- and hyperthyroidism. When both TPOAb and TgAb were present, individuals were 23 times more likely to have clinical hypothyroidism and 12 times more likely to have subclinical hypothyroidism. In the population of those with both antibodies and a TSH over 2.5, there was a 40-fold increased risk of having clinical hypothyroidism.[14]

In addition to the recognized effects of infectious agents, medications (iodine, amiodarone, lithium), and stress, environmental toxins have been implicated in the genesis of TAD. In men and women from a PCB-polluted area in Slovakia, those with highest blood PCB levels compared with the lowest blood PCB levels (5th quintile compared to the 1st quintile) had significantly higher TPOAb. Twenty-eight percent of male workers in the highest quintile of blood PCB levels had TPOAb as opposed to only 20 percent of those in the lowest quintile.[22] Women who were occupationally exposed to PCBs had significantly higher TPOAb, TgAb, and TSH-receptor stimulating antibody titers than women who lived in the area but were not exposed occupationally.[22]

In other studies, PCB, dioxin, and heavy metal exposures have also been associated with increased levels of both TPOAb and TgAb in residents living near waste sites[23] and in large populations exposured to PCBs from rice bran oil contamination.[24]

The Akwesasne Mohawk Nation is located in a highly polluted area near the St. Lawrence River in upstate New York and Quebec, Canada, downstream from two National Priority List Superfund sites. Because the Akwesasne are a culture who historically rely on locally-caught fish consumption (a significant source of PCBs), youth were studied to assess the effects of PCBs and other endocrine disruptors on levels of TPOAb.[25] Fifteen percent of 115 youths (ages 10-17) studied had elevated TPOAb; 23 percent of the females and nine percent of the males. Among those who had been breast fed, TPOAb was positively correlated with higher serum levels of persistent PCBs, dichlorodiphenyldichloroethylene (DDE), hexachlorobenzene (HCB), and mirex. No effects of the environmental contaminants were evident among non-breast-fed young adults.

Antibody presence does not equal autoimmune pathology or affect T4 or TSH levels, as was the case in NHANES III where 18 percent of the "disease-free population" had evidence of TPOAb or TgAb.[7] Recent research, however, has shown the presence of TPOAb has a significant predictive value. In one study, elevated TPOAb in postpartum women measured at the time of birth had a 92-percent positive predictive value for the onset of disease 7-10 years later.[26]

Thyroid Metabolism/Fetal Development and Risk for Cardiovascular Disease in Adults

In humans, thyroid hormone (both T3 and T4) is important for normal development of the central nervous system, pulmonary system, cardiovascular system, and other organs.[27]

Neurodevelopmental effects have been seen with changes in circulating levels of thyroid hormones, and the most crucial window of development is the first trimester of pregnancy, where overt or subclinical hypothyroidism in the mother can result in impaired intellectual development in her children.[28,29] Women with high levels of TPOAb had a six-fold increased risk of presenting with relatively low free T4 levels in early gestation, which is also a risk factor for impaired psychomotor development in the offspring.[30]

Small differences, approximately 25 percent, of maternal T4 during the early fetal period are associated with reduced IQ scores and other adverse effects, even when mothers had TSH and total T4 levels in the standard normal range.[31,32] These findings have also been confirmed in animals, specifically when transient changes in serum T4 can result in brain damage and hearing loss.[33]

Thyroid hormone deficits in adults are correlated with adverse effects in organ systems; recent research has focused on the cardiovascular system and serum lipids.[34,35]

One study of elderly women found a 2.3-fold greater risk of myocardial infarction in those with subclinical hypothyroidism (95% CI: 1.3-4.0) and a 1.7-fold increased risk of aortic atherosclerosis (95% CI: 1.1-2.6). A meta-analysis of subclinical hypothyroidism and ischemic heart disease found a significant relationship between the two in women under age 65.[36] Total cholesterol, low-density lipoproteins (LDL), non-high-density lipoproteins (non-HDL), and triglycerides increased linearly with increasing TSH, and HDL decreased consistently with increasing TSH within normal reference ranges.[37] Intimal medial thickness and flow-mediated dilation, both measures of atherosclerosis and predictive of coronary vascular disease, have been shown to be inversely related to thyroid hormones within the normal reference range.[38,39]

A recent Spanish population study of cardiovascular risk factors found TSH ≥2.5 mU/L was positively associated with body mass index, total cholesterol, and homocysteine levels.[40]

A meta-analysis of research on subclinical hypothyroidism and risk for cardiovascular disease (14 epidemiological studies) found a 65-percent increased risk for coronary artery disease with elevated TSH and normal free T4.[41] Studies of thyroxine replacement also show improvement in lipids in those with both high normal TSH and elevated TSH (subclinical hypothyroidism).

Treatment with T4 of hypercholesterolemic individuals significantly reduced both total and LDL cholesterol most effectively in those with "high-normal" levels of TSH (2.0-4.0 mU/L).[42]

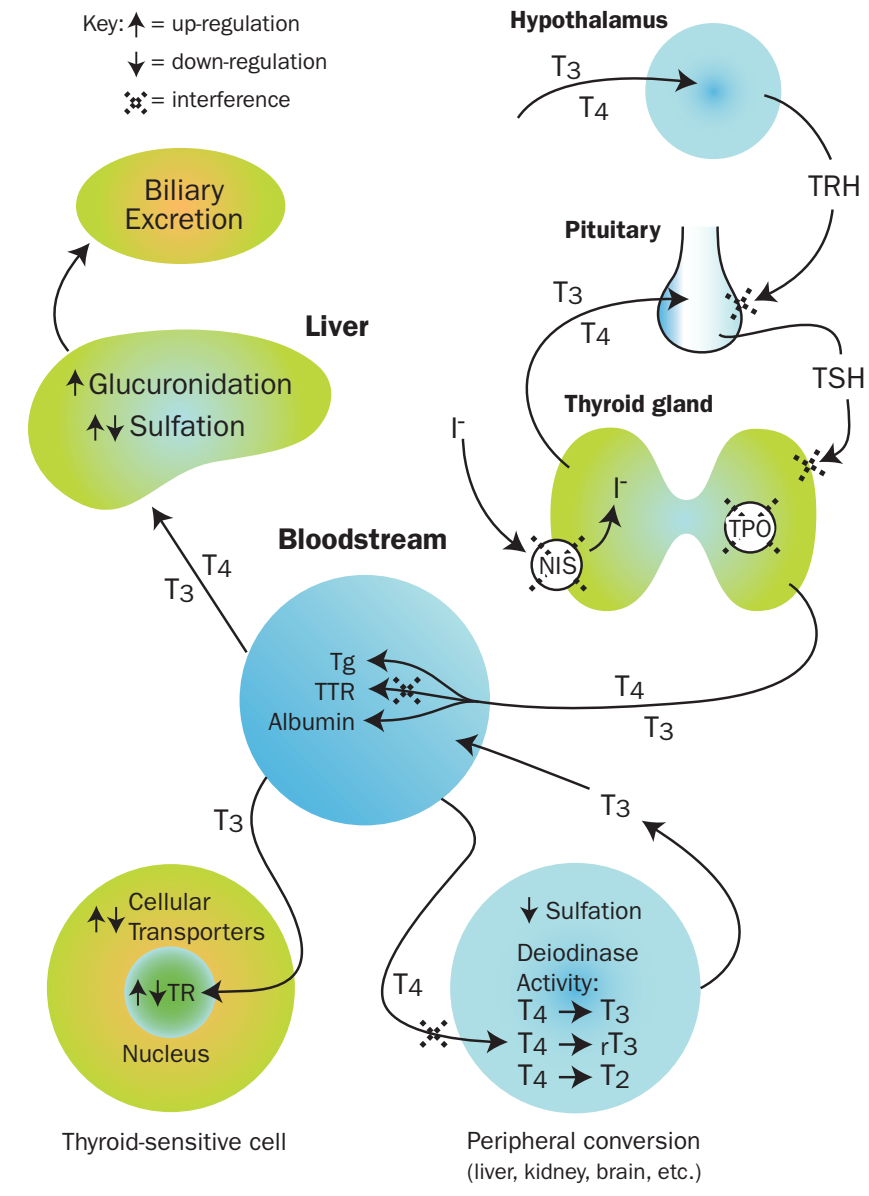
A thyroxine-replacement study in women with subclinical hypothyroidism demonstrated effectiveness in lowering LDL cholesterol and decreasing cardiovascular risk by 9-31 percent.[43]

Thyroid Disruptors and Effects on Specific Stages of Thyroid Metabolism

The implications for treating thyroid hormone abnormalities as evidenced above become more complicated in the context of thyroid disruption, as the mechanisms of altering thyroid function affect every aspect of thyroid metabolism (Figure 1).

The primary environmental chemicals identified as thyroid disruptors are PCBs, bisphenol A (4,4' isopropylidenediphenol or BPA), perchlorate, tetrachlorodibenzo-p-dioxin (TCDD) and polychlorinated dibenzofuran (PCDF) (both commonly referred to as dioxins), pentachlorophenol (measured in mammals as the source chemical hexachlorobenzene, a common pesticide that breaks down into pentachlorophenol), triclosan, polybrominated diphenyl ethers (PBDEs) and tetrabrominated diphenyl ethers commonly known as flame retardants, and naturally-occurring chemicals such as soy isoflavones and thiocyanate in cruciferous vegetables.[6] Phthalates (di[2-ethylhexyl] phthalate [DEHP], di-n-octyl phthalate [DnOP], diisodecyl phthalate [DIDP], di-n-hexyl phthalate [DNHP], and di-n-butyl phthalate [DBP]), used as plastic emollients in feeding tubes and plastic containers, have also been shown to alter thyroid function in animal studies.

Figure 1. Thyroid Disruptors: Effect at Various Stages of Thyroid Metabolism



TTR = transthyretin, Tg = thyroglobulin, TSH = thyroid-stimulating hormone, TRH = thyrotropin-releasing hormone, TPO = thyroperoxidase, NIS = sodium-iodide symporter

There is also increasing evidence that parabens (used in cosmetics) and pesticides (dichlorodiphenyltrichloroethane [DDT], HCB, methoxychlor, chlordane, and endosulfan) have thyroid-disrupting effects in animals and humans. The most commonly used biomarker in studies of effect for TD exposure is serum total T4 concentrations, even though, as stated above, free T4 levels are more accurate at determining thyroid status. And, although TSH is a well-accepted biomarker for hypothyroidism, a number of xenobiotics alter circulating thyroid hormone levels but do not change TSH.[44]

Thyroid disruptors can affect thyroid physiology in many phases of thyroid regulation. The complex system of iodine uptake, thyroid hormone production, interconversion of thyroid hormones, cellular uptake, cell receptor activation, and hormone degradation and elimination can be directly altered by thyroid disruptors.[6] In addressing what is known about TD effects, it is helpful to review hormone metabolism and the complex loops involved in the thyroid-hypothalamic-pituitary axis (Figure 1).

Thyroid hormone production is highly regulated by negative feedback systems that involve the hypothalamus, pituitary, and the thyroid gland itself. Thyrotropin-releasing hormone (TRH), secreted by the hypothalamus, binds to TRH receptors in the pituitary thyroid-sensitive thyrotrope cells that, in turn, secrete TSH. TSH production is also stimulated by the direct effect of T3 and T4 binding to the thyrotrope cells.[45,46]

TSH is secreted into circulation and binds to the TSH receptors in the thyroid gland, stimulating the production of thyroglobulin, thyroid peroxidase, sodium-iodide symporter (NIS) protein, and thyroxine.[47]

Table 1. Mechanisms and Effects of Thyroid Disruptors[55,60]

Thyroid Disruptors	Mechanism	Effect
Perchlorates, thiocyanate, nitrate, bromates, phthalates	Blocking uptake of iodide into thyroid cell	Decreased synthesis of T3 and T4
Methimazole, amitrole, soy isoflavones, benzophenone 2	Blocking production of TPO in thyroid follicles	Decreased synthesis of T3 and T4
PCBs, pentachlorophenol, flame retardants, phthalates	Competitive binding to thyroid transport protein (TTR)	Possible effect on fetal brain T4 production
Dioxin, PBDE, chlordane	Altering transport across cell membrane	Increased biliary elimination of T3 and T4
Acetochlor (herbicide), PCBs	Enhanced hepatic metabolism	Increased biliary metabolism of T3 and T4
PCBs, triclosan, pentachlorophenol, dioxin, difuran	Inhibition of sulfation	Decreased sulfation of thyroid hormones leading to possible decrease of peripheral T3 synthesis
FD&C red dye #3, PCBs, octyl-methoxycinnamate	Inhibition of deiodinase activity	Decreased peripheral T3 synthesis
PCBs, bisphenol A, hexachlorobenzene, flame retardants	Altering binding to thyroid receptor	Altered thyroid hormone directed gene transcription
DDT, PCBs	Inhibiting TSH receptor	Decreased production of T3 and T4

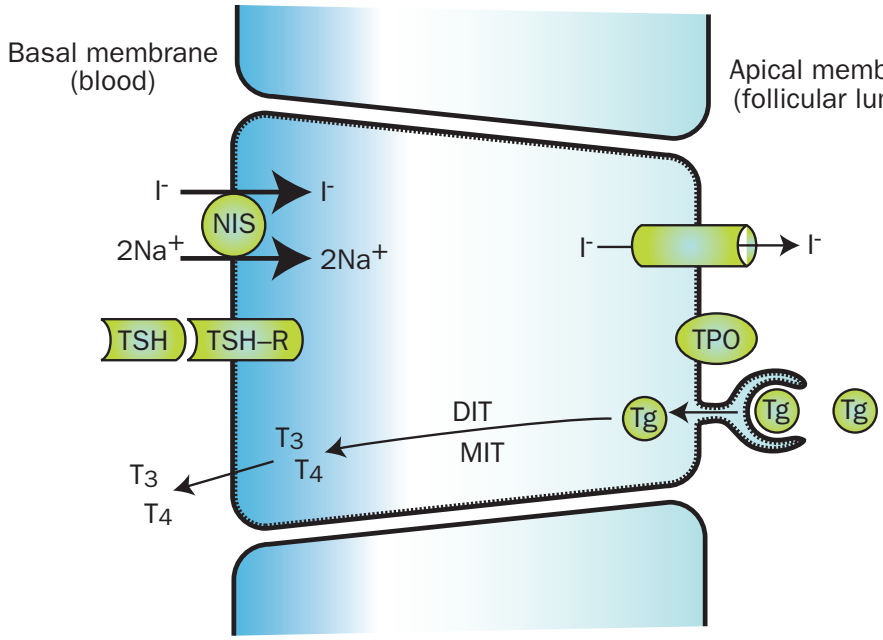
The Sodium-Iodide Symporter Protein and Iodine Uptake in the Thyroid Gland

In thyroid tissue, TSH-stimulated iodine uptake is facilitated by a mechanism that allows thyroid tissue to concentrate iodide molecules at levels 20-40 times greater than that found in the plasma. This is facilitated by a plasma membrane transport protein NIS.[48] NIS is located on the outer membrane of the thyrocyte and allows sodium to be pumped out of the follicular cell while iodide is pumped into the follicular cell. NIS activity is sensitive to both iodine availability and TSH stimulation and, without it, iodine would not be imported into the follicular cells in high enough concentrations to produce adequate amounts of thyroxine.

NIS is also found in mammary cells, cervical cells, gastric mucosa, choroid plexus, and saliva, where it facilitates the uptake and concentration of iodine in these cells as well.[49]

The effect of TDs on the NIS receptor protein has been shown with perchlorate (detailed below), thiocyanate, bromate, and nitrate.[50] These compounds compete with iodine for binding to the NIS protein and thereby inhibit the uptake of iodine into the follicular thyroid cell. The observed effects of these TDs on thyroid hormone are decreased synthesis of T4 and T3.[51] Table 1 outlines mechanisms and effects of thyroid disruptors.

Figure 2. Intrathyroidal Iodine Metabolism



MIT = mono-iodothyronine, DIT = di-iodothyronine, Tg = thyroglobulin, TPO = thyroperoxidase, NIS = sodium-iodide symporter, TSH = thyroid-stimulating hormone

Iodide enters the follicular cell via the NIS protein and is attached to Tg in the presence of TPO. Tg then enters the follicular cell, discharging DIT and MIT, which are the building blocks of T3 and T4.

Adapted from: Boas M, Feldt-Rasmussen U, Skakkebaek NE, Main KM. Environmental chemicals and thyroid function. *Eur J Endocrinol* 2006;154:599-611.

Evidence that the expression of the NIS protein is up-regulated in hyperthyroidism and Graves' disease and down-regulated in adenomas and carcinomas has lead to interest in how the presence or absence of the NIS protein or effects on NIS activity are related to carcinogenesis.[52,53]

The Production of T3 and T4 in the Thyroid Gland

Once iodide molecules are transported into the thyrocyte, they are bound to tyrosine residues in thyroglobulin molecules as either mono-iodothyronine (MIT) or di-iodothyronine (DIT).

T4 and T3 are produced through a series of peroxidation reactions with tyrosine residues that require iodide (in the form of mono- and di-iodothyronine), a supply of hydrogen peroxide, the enzyme thyroperoxidase (TPO), and an iodine acceptor protein – thyroglobulin (Tg).[54] TPO performs the function of reducing hydrogen peroxide so it can oxidize iodine, allowing iodide molecules to attach to the tyrosyl residues of the thyroglobulin molecule, forming mono- and di-iodothyronine. Two DIT molecules form T4; one DIT and one MIT form T3. The reaction is catalyzed by TPO, which requires the presence of hydrogen peroxide (Figure 2).

The NIS transport protein, Tg, TPO, the production of hydrogen peroxide (H_20_2), and the intrathyroidal formation of T3 relative to T4 are all stimulated by the presence of TSH.

Specific TDs have also been found to inhibit the formation of TPO, thereby altering the ability of the follicular cell to produce T4, and consequently T3, even in an environment of adequate iodide and NIS transport proteins. Amitrole (herbicide), ethylenethiourea (fungicide), mancozeb (fungicide), soy isoflavones, and benzophenone 2 (ingredient used as a sunscreen in cosmetics) have been shown in animal studies to inhibit TPO production and prevent the synthesis of thyroglobulin, thus decreasing synthesis of T3 and T4 (Table 1).[55]

Transport of Thyroid Hormones in the Bloodstream

Once in the bloodstream, thyroid hormones are either bound to three transport proteins – thyroid binding globulin (TBG), transthyretin (TTR), or albumin – or they circulate freely in the plasma. The amount of free hormone is relatively small compared to what is bound: less than 0.5 percent of circulating hormone is in the free fraction. TBG binds 75 percent of serum T4, while TTR binds 20 percent, and serum albumin only binds five percent or less of the remaining T4 in circulation.[56] However, TTR is the major thyroid transport protein in the human brain, playing a crucial role in the determination of free T4 levels in the extracellular compartment of brain tissue, which is independent of T4 homeostasis in the body. TTR may also mediate the delivery of T4 across the blood-brain barrier and facilitate maternal-to-fetal transport through the placenta.[57]

Since the hormone must be in the free state to be taken into the cell, free state levels more accurately reflect thyroid function. Transport proteins, therefore, maintain a large extrathyroidal pool of T4 and T3 hormone available for cellular use. If binding proteins were not available, the small pool of extrathyroidal hormone would be depleted within a matter of hours, and conversely if thyroid hormone production were to stop for 24 hours, the amount of T4 and T3 in the extrathyroidal pool would decrease by only 10 and 40 percent, respectively.[58] This binding of iodine to a macromolecule in the bloodstream may serve multiple functions, including the ability to decrease urinary wasting of iodine and to target the amount and timing of hormone delivery that is site-specific, particularly the central nervous system.[59]

PCBs, flame retardants, phthalates, and pentachlorophenol (a pesticide metabolite and wood preservative) have been found to bind to TTR. These chemicals, bound to TTR, may be transported to the fetal compartment and fetal brain, with a resultant decrease in fetal brain T4 levels.[60]

Deiodinase Enzymes and Cellular Thyroid Hormone Regulation

T3 is considered the bioactive form of thyroid hormone, while T4 is mainly a prohormone that becomes activated upon its conversion to T3. To exert its biological action, T3 must first bind to the nuclear receptor in target cells. Nuclear bound T3 is partly derived from plasma and partly from local generation as a result of the deiodination of T4. For biological action of thyroid hormone, both T3 and T4 have to cross the plasma membrane of target cells. Cellular thyroid hormone transporters (OATP1C1, MCT8) allow for the movement of thyroid hormones across cellular membranes and are necessary for cellular entry and exit of both T3 and T4. Once inside the cell, T3 is bound to nuclear thyroid receptors that act as signal transducers to initiate intranuclear changes in cell metabolism.[61]

Specific TDs (flame retardants, PCBs, bisphenol A, dioxin) have been found to both inhibit or activate the cellular uptake of thyroid hormone, leading to possible increased biliary excretion of T3 and T4 and to changes in the nuclear thyroid receptor activity, resulting in altered gene transcription. This would be particularly damaging in the developing brain. In addition, TSH and TRH binding have been shown to be adversely affected by TDs. The mechanism may be receptor-binding inhibition or other mechanisms that prevent TSH and TRH from exerting effects on up-regulation of cellular metabolism and production of T3 and T4.[60,62]

Thyroid hormone levels are also controlled by three different deiodinase enzymes responsible for the production and recycling of T3 and T4 inside specific types of cells (Table 2). The type I iodothyronine 5'-deiodinase (D1) is produced mainly in the liver, kidneys, and thyroid, but has also been isolated in pituitary and cardiac tissue. In the liver, the hepatic enzyme is thought to be the main source of peripheral T3 production and the main site for the clearance of plasma reverse T3 (rT3). D1 has known sensitivity to inhibition by the anti-thyroid drug propylthiouracil (PTU) and other chemical thyroid disruptors.[63,64]

In the thyroid, D1 deiodinates about 10 percent of T4 to T3. The extent of this intrathyroidal deiodination is increased when the thyroid is stimulated by TSH. About 70 percent of the thyroglobulin-bound iodine content in the thyroid is in the form of DIT and MIT, which is efficiently recycled by D1 and serves as an important source of T4. There are individuals who do not have thyroidal D1 due to congenital loss of the enzyme and thus cannot deiodinate iodotyrosines, resulting in goiters that respond to treatment with iodine.[65]

Table 2. Local Control of Thyroid Hormone Regulation: Deiodinase Enzymes and Sulfation

Iodinase	Tissue Produced In	Function
Type I deiodinase	Liver, kidney, thyroid, pituitary, heart	Local synthesis of T3 and T4 in thyroid; peripheral synthesis of T3; breakdown of rT3
Type II deiodinase	Pituitary, brain, skeletal muscle, brown adipose	Regulates and insures adequate local T3 production; adds to systemic T3 production
Type III deiodinase	Placenta, uterus, brain, fetal tissues, thyroid, kidney, adult liver, possibly other tissues	Inactivation of T3; facilitates T4 to rT3

The D1 activity in liver and kidney is stimulated in hyperthyroidism and decreased in hypothyroidism as a result of the positive feedback of T3 on D1 production.[66]

Rats raised on a severely selenium-deficient diet have a dramatic reduction in liver and kidney D1 activity, as D1 is more dependent on selenium availability than type II deiodinase (D2) or type III deiodinase (D3). These rats showed a significant decrease in serum T3 and an increase in serum T4, due to the important role of D1 in peripheral T4 to T3 conversion.[67]

D2 is produced in the central nervous system including the pituitary, skeletal muscle, cardiac muscle, and brown adipose tissue. D2 is active in maintaining T3 levels in these tissues, particularly in the face of changing plasma T4 and T3 levels.[68-70] Plasma T3 levels are to a large degree determined by D1 activity in liver and kidneys, but the brain uses D2 for local T3 production, which allows specific delivery of T3 to neurons and astrocytes independently of plasma T3 levels.[71,72] This mechanism is used in the developing fetus as a way to ensure adequate levels of T3 in the development of the cochlea, a mechanism affected by the presence of PCBs.[33,62]

The location of D2 in the skeletal muscle provides another source of plasma T3 in addition to D1 conversion in the liver and kidneys. Because D1 is regulated by positive feedback and D2 is regulated by negative feedback mechanisms, their relative contributions to plasma T3 production may depend on thyroid state. D2 activity is significantly stimulated in Graves' disease via both TSH and TSH-receptor antibodies.[68] Follicular thyroid carcinoma may express high levels of D2, in one case resulting in highly elevated serum T3 levels.[73]

D3 is produced in the brain and plasma and facilitates the degradation of T3 or the deiodination of T4 to rT3 in order to provide a consistent T3 supply to the adult and fetal brain. Normally about one-third of T4 is converted to T3 and about one-third to rT3. High D3 activities have been seen in the placenta, the pregnant uterus, and in fetal tissues.[74] D3 levels are usually much higher in fetal than in adult tissues, where this mechanism is believed to prevent excess stimulation by T3 that might otherwise result in abnormal cellular differentiation.[75]

D3 activity is also highly expressed in certain tumors, including hepatocarcinomas, hemangiomas, and basal cell carcinomas.[76-78]

PCBs (see section below), FD&C red dye #3, octylmethoxycinnamate (an ultraviolet light-blocking agent used in cosmetic sunscreens), the pesticide methoxychlor, and the toxic metals lead and cadmium have been shown to interfere with the action of the deiodinase enzymes.[60] The effect of this alteration of deiodinase activity decreases peripheral synthesis of T3.[62]

In addition to deiodination, thyroid hormones are metabolized in the liver and kidneys by conjugation with sulfate or glucuronic acid as diphosphoryl glucuronosyltransferase (UGT) or sulfotransferase (SULT) isoenzymes. Sulfation and glucuronidation are phase

2 detoxification reactions, a process that increases the water-solubility of the substrates and allows for their biliary and urinary clearance.[79]

Sulfation and sulfotransferases are also found in the intestine, uterus, mammary gland, and brain where they initiate the irreversible degradation of T4 and T3 by D1, providing an important regulatory function.[80] Sulfation is a reversible process and sulfated thyroid hormone can be reversed by sulfatases, either in tissues or by sulfatase produced by intestinal bacteria.[81] In the fetus, sulfated T3 may be retained as a reservoir for active T3.[82]

TDs (PCBs, triclosan, pentachlorophenol, dioxins) inhibit the activity of sulfotransferases, resulting in decreased sulfation and dysregulation of peripheral T4 and T3 levels, as would be expected from the active role the enzymes play in brain, uterine, mammary, and intestinal thyroid hormone regulation.[60,62] TDs (acetochlor, PCBs, dioxins, bisphenol A) also up-regulate UGT hepatic catabolism,[3] resulting in increased biliary elimination of T3 and T4.[62]

Summary of Mechanisms of Thyroid Disruption

In summary, the basic areas of interference with thyroid metabolism (Figure 1) are: (1) inhibition of iodide uptake at the cellular membrane of the thyrocyte via blockage of the NIS transporter; (2) synthesis inhibition via thyroperoxidase; (3) binding of transport protein TTR in the bloodstream; (4) altered hepatic phase 2 catabolism by glucuronosyltransferase and sulfotransferase metabolism of T3 and T4; (5) alteration of deiodinase-regulated T4 metabolism; and (6) alterations of transport across cellular membranes and alteration of cellular receptors (TSH receptor). Although these mechanisms refer to animal models, the effect of TDs has been extensively studied in humans, particularly the effects of perchlorate and PCBs discussed below.

Perchlorates as Thyroid Disruptors

Perchlorate is one of the best researched thyroid-disrupting chemicals. Perchlorates are found naturally in soil and Chilean nitrate-based fertilizers (perchlorate levels in the water in Chile have been found to be as high as 100-120 mcg/L).[5] Perchlorate has also been manufactured as a pharmaceutical used in the treatment of hyperthyroidism and as an industrial oxidizer in propellants for rockets, missiles, and air bag inflation systems.[83,84] Perchlorate has been found in significant levels in municipal water systems in the United States and is actively transported into breast milk where relatively high levels have been reported in the United States and Chile.[85]

Recent studies have found significant perchlorate contamination in groundwater throughout the western United States as a result of ammonium perchlorate disposal and leaching from industrial and waste storage sites. Perchlorate (at levels over 4 ppb) has been found to contaminate the drinking water of 11 million people in the United States. High levels of perchlorate have also been found in the food supply with the result that breast milk contains five times the perchlorate levels (10.1 mcg/L) of cow milk (2 mcg/L).[86] Perchlorate contamination has also been documented in grain, fruit, vegetables, dietary supplements, and forage crops for livestock.[87-89]

In an extensive review, Brucker-Davis cites 49 studies on the effects of perchlorate as a thyroid disruptor in animal models.[3] Perchlorate is a known competitive inhibitor of the sodium-iodide symporter in humans and can inhibit iodide uptake, leading to the suppression of T3 and T4.[51] The NIS uptake mechanism is also found in mammary tissue and perchlorate has been related to lower levels of iodine in breast milk, a risk factor for neurodevelopmental disorders that occur *in utero* as a result of iodine deficiency.[51] Due to the recent evidence that perchlorate contamination of food and water is a widespread phenomenon, attempts have been made to evaluate the effect of perchlorate contamination on thyroid function in the general population.

In the NHANES study of 2,820 U.S. residents from 2001-2002, levels of perchlorate were detectable in the urine of all 2,820 participants.[90] Of those who were female and over the age of 12, 35 percent had urine iodine concentrations <100 mcg/L. The cutoff value of urinary iodine at <100 mcg/L was chosen because the World Health Organization designates <100 mcg/L urinary iodine as a median level that indicates a prevalence of goiter in a population due to dietary iodine insufficiency.[91] In this subset of females, increasing levels of urinary perchlorate were predictive of a significantly lower serum T4 ($p<0.0001$) and a significantly higher

Alternative Medicine Review Volume 14, Number 4 2009

serum TSH level ($p<0.0010$). In women with urinary iodine levels >100 mcg/L, urine perchlorate was not a significant predictor of serum T4, but was a significant predictor of serum TSH. In other words, rising levels of urinary perchlorate predicted higher levels of TSH in women with normal serum T4 (5.0-12.0 mcg/dL) and serum TSH (0.3-4.5 mU/L). The unique aspect of this study is that the levels of urinary perchlorate in this cohort of women were the lowest of any prior study, with median levels of 3.38 mcg urinary perchlorate/g creatinine and a 95th percentile of 14 mcg/L (12.7 mcg/g creatinine).[92,93]

In contrast, other studies of perchlorate exposure have not found a significant relationship to thyroid parameters. Pearce et al found no change in thyroid function in a small study of first trimester pregnant women in Europe whose urinary iodine levels were <100 mcg/L.[94] However, pregnancy up-regulates thyroid function in a way that may have had a confounding effect. Other studies of low-dose perchlorate exposure for limited periods of time found no relationship of urinary perchlorate to thyroid metabolism. These were studies that did not isolate or identify women with urine iodine levels below 100 mcg/L.[95-98]

Other NIS competitors include nitrate and thiocyanate. Combining these with perchlorate may have cumulative effects. Nitrate is found naturally in green leafy vegetables, as a preservative in processed meat and fish, and as a contaminant from mineral fertilizers.[50] Elevated levels of as much as 973 mg nitrate per kg fresh weight have been found in iceberg lettuce samples. Thiocyanates, the result of the metabolism of free cyanide found in foods (Brassicaceae family, cassava, sweet potatoes, corn, apricots, cherries, almonds) and as preformed thiocyanate in cigarette smoke, also block NIS uptake. The breast milk from mothers who were daily smokers contained half the iodine when compared to nonsmoking mothers, linked to the thiocyanate in the cigarette smoke that blocked iodine uptake into mammary tissue.[99] An epidemiological study in Germany found that thiocyanate levels, when combined with urinary iodide levels, were more predictive of the prevalence of goiter than urinary iodine alone.[100]

When the NHANES study cited above[90] looked at the relationship of thiocyanate from smoking, perchlorate, and low urinary iodine together, it found a significantly greater effect of perchlorate on serum T4 in smokers compared to nonsmokers, thought to reflect the cumulative effect of perchlorate and thiocyanate.[93] This was particularly evident in those women who had urinary perchlorate levels over the mean of 3.38 mcg/g creatinine.

In the NHANES study, the 95th percentile of the distribution of estimated daily perchlorate doses in the adult population was 0.234 mcg/kg/day and was below the EPA reference dose (0.7 mcg/kg/day), a dose estimated to be without appreciable risk of adverse effects during a lifetime of exposure.[90] That reference dose, however, does not take into consideration that thyroid disruptors have dose-dependent effects that are synergistic when added to other thyroid disruptors having the same NIS-blocking action.

In an environment with exposure to nitrate, thiocyanate, the herbicide amitrole, the fungicide ethylenethiourea, and other environmental TDs like mancozeb and benzophenone that block NIS uptake of iodine, perchlorate exposure within the "safe reference dose" may have a significant effect on thyroid hormone production, particularly in the environment of dietary iodine insufficiency.[101]

PCBs as Thyroid Disruptors

The Stockholm Convention on Persistent Organic Pollutants is an international treaty that operates under the auspices of the United Nations to control certain chemicals considered to be persistent organic pollutants, also known as persistent, bioaccumulative, and toxic substances (PBTs). In 2001, more than 100 countries signed the Convention, committing to discontinue or restrict use of 12 chemicals of concern (PCBs are included). The United States, along with other countries like Bosnia, Kazakhstan, Guinea, and Belize, have yet to ratify the Convention.[102]

Polychlorinated biphenyls belong to the class of organochlorine compounds classified as persistent organohalogenated pollutants (POPs) that include dioxin (polychlorinated dibenzodioxin or PCDD), PCDFs, fire retardants (PBDEs), bisphenol A, and pesticides and herbicides hexachlorobenzene, DDT, and DDE. PCBs were discovered before the turn of the century and were used in U.S. industry in electronics manufacturing as coolants or heat transfer agents until their use became highly restricted in 1977. PCBs were used in the manufacture of hydraulic fluids, lubricants,

paints, wax extenders, plasticizers, inks, adhesives, pesticide extenders, flame retardants, carbonless copy paper, wire insulators, caulking materials, and heat insulation. Their use was phased out because of their carcinogenic potential.[103]

Because they are resistant to molecular degradation, PCBs are persistent in the environment; about 1.5 million metric tons are now distributed over the surface of the earth. The most polluted areas of the earth are called "PCB reservoirs" and include the Baltic Sea, Hudson Bay, and the Great Lakes.[104] PCBs can "biomagnify" (increase more than would otherwise be found as a result of bioconcentration as PCB accumulation increases higher in the food chain) as much as 1,000,000 times from the level in contaminated water to its concentration up the food chain.[3]

PCBs exist in a variety of what are referred to as congeners – paired phenyl rings with various degrees of chlorination. There are 209 possible congeners that have been synthesized but less than 50 that are considered environmentally threatening and fewer than 25 that account for the majority of the burden in animals and humans. The effects of PCBs are congener-specific (relating to the number and structural relationship of chlorine atoms in the PCB molecule). PCBs with a higher degree of chlorination at the meta- and para- positions are more metabolically persistent in human and animal tissue and have a structural similarity to thyroxine.[104] They are associated with immune damage, thyroid toxicity, cancer, and neurodevelopmental deficits in animal models, as well as directly lowering circulating levels of thyroid hormones.[105] The skin, liver, gastrointestinal tract, immune system, and nervous system are affected by exposure in humans and animals.[106]

Sources of PCBs are meat, fish (farmed fish or fish from the Great Lakes have documented high PCB levels), and dairy products.[107,108] PCB levels (along with levels of toxaphene and dieldrin) in fish, including wild salmon from Alaska, have led to consumption advisories (in recommended maximum meals per month) for fish obtained worldwide (Figure 3).[109]

Contaminated caulk in commercial buildings and schools built before 1980 has recently been recognized as a significant source of exposure.[110] The use of PCB-containing caulking material containing Aroclor was a common construction practice in the 1970s. In an investigation of teacher exposures to PCBs in German schools, inhalation of PCB-containing dust has been shown to contribute to elevations of blood levels of PCBs.[111,112] Because PCBs are lipophilic, they concentrate and are measured in human adipose tissue and in blood as a fraction of blood lipids.

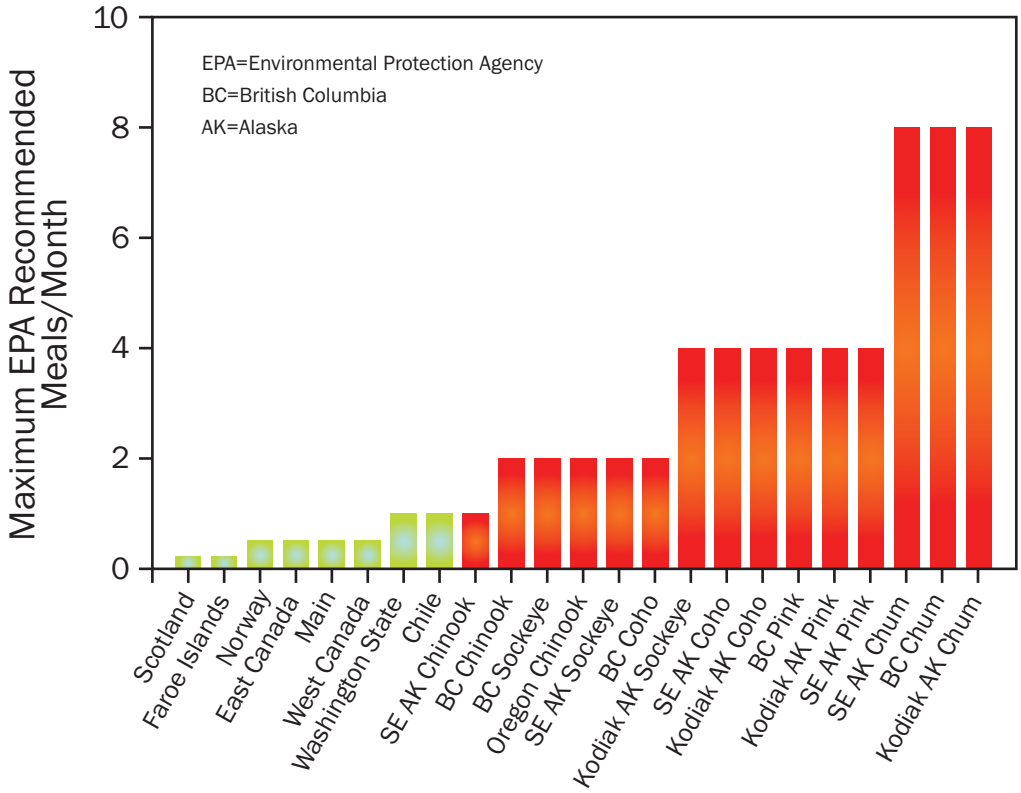
The average half-life for the more toxic PCB congeners is stated to be as much as seven years,[113] but elevated adipose lipid levels were documented 30 years post-exposure in cases of ingesting PCB-contaminated rice oil that occurred in Japan, referred to as the "Yusho" PCB poisoning.[114]

PCBs have been shown to affect thyroid function through several different mechanisms previously reviewed: (1) reducing the ability of thyroid hormones to bind to transport proteins in the bloodstream; (2) enhancing hepatic metabolism by up-regulating the glucuronosyltransferases or sulfotransferases that break down thyroid hormones in the liver; (3) inhibiting or up-regulating the production of deiodinases that allow T4 to be converted to T3; and (4) acting as either an agonist or antagonist at the site of the cellular thyroid receptor.[62,105,115-118]

Interference with the deiodinases that allow for T4 conversion to T3 (D1) or from T4 to rT3 and T3 to T2 (D3 catalyzes both reactions) in peripheral sites, has been hypothesized to be the cause of a relationship between serum PCB levels and lower levels of total T3 found in some studies.[119] There is also evidence that PCB congeners can mimic thyroid hormone's effect on gene expression in the brain.[120] PCBs appear to interfere with the binding of prealbumin to T4 and can limit its availability in the brain, a concern in the neurodevelopment of neonates.[121,122] Likewise, PCBs have been shown to bind to the thyroid transport protein TTR, which is believed to be necessary for the delivery of T4 across the blood-brain barrier and across the placenta to the fetus.[123]

Although PCBs are present in human breast milk in every part of the world where studies have been conducted, levels are highest in industrialized countries, leading to the identification of human breast-fed infants in these countries as a "special risk group."[104] Because of their weight, growth rates, and ingestion of relatively high PCB levels per calorie of breast milk, infants are considered the most highly exposed population. They are at greatest risk from the adverse effects of organochlorine pollutants, including neuropsychological

Figure 3. Consumption Advisories for Maximum Recommended Meals per Month Based on PCB, Toxaphene, and Dieldrin Content



Consumption advisories in meals per month based on U.S. EPA cumulative risk assessment methods for PCBs, toxaphene, and dieldrin for farmed (red) and wild (green) salmon.

Adapted from: Hites RA, Foran JA, Carpenter DO, et al. Global assessment of organic contaminants in farmed salmon. *Science* 2004;303:226-229.

disorders, delayed neurodevelopment, immune dysfunction (decreased IgA, IgM, and total, cytotoxic, and suppressor T-cell counts), increased frequency of pulmonary disease, middle ear infections, and greater susceptibility to mumps and measles.[124-128]

The exposure effect of PCB, TCDD, and PCDF is expressed as total toxic equivalents (TEQs). TEQs was developed to compare exposure levels of different populations to organochlorine pollutants, specifically dioxins, difurans, and PCBs. The daily toxic equivalency factor (TEF; used to measure TEQs) for an adult in New York has been estimated to be between 0.3 and 3.0 TEF/kg body weight, while the TEF for a breast-fed infant in the United States has been estimated at 35-53 TEF/kg body weight.[129]

In addressing the effects of PCBs and dioxins in pregnant women, infants, and children, many, but not all, epidemiological studies of maternal exposure have been associated with changes in thyroid hormone levels and related deficiencies in psychomotor development of infants.

Because the damaging effects of very small changes in prenatal thyroid levels (2.6 ppt of free T4 in the mother's blood) on neurodevelopment and IQ may occur even within normal lab reference ranges, studies attempting to define direct effects of PCBs on mother and infant thyroid levels provide inconsistent results.[75,126,130-133]

A study of mothers with low background level exposure to PCBs in California's Salinas Valley found that levels of specific PCB congeners (PCB 99, 138, 153, 180, 183, 187, 194, 199) were positively associated with rising neonatal TSH levels.[134]

In a study of 259 four-year-old Spanish children with background exposure to PCBs, DDT, and HCH, serum levels of PCBs were related to lower total T3 levels and one of the PCB congeners – PCB-118 – was inversely associated with free T4 levels.[119]

Schantz conducted a thorough review of the literature on PCBs and neurodevelopmental effects and found that studies from Taiwan, Michigan, New York, Holland, Germany, and the Faroe Islands were consistent in reporting prenatal PCB exposures and negative effects on cognitive function in both infancy and childhood.[135] Due to high dietary intakes of fish in the Faroe Islands group, the researcher found that the strongest association with PCBs and decreased neuropsychological scores was seen in the cohort with the highest mercury exposure. Mercury is a known thyroid toxicant and may have had a significant additive effect in the Faroe Island cohort, although a later National Academy of Sciences panel ruled that effects of the two pollutants are able to be separated based on exposure levels and developmental effects.

In general, most studies of PCB exposure in adults (occupational exposure, high fish consumption, living near a pollution source) have shown an inverse relationship between PCB levels and serum T4 levels or TSH levels,[136-139] although one study of adults from a heavily polluted area in Slovakia revealed a positive relationship between serum PCB levels and free T3 and free T4.[104]

As part of the 1999-2002 NHANES, assays for 20 PCBs, total dioxins, and furans were performed in 1,166 males and 1,279 females.[140] In looking at the dioxin-like TEQs (levels of total toxicity resulting from the toxicity of individual PCB congeners, dioxins and furans), higher TEQs were related to lower levels of total T4, particularly in women. The effects of PCBs on increasing TSH and decreasing T4 were stronger in women over age 60. Most significant was the relationship of higher PCB levels to lower TSH levels in men over age 60. Although there is no way of knowing the additive effect of dioxin and furan exposure, other U.S. studies of background exposure have concluded that PCBs contribute substantially more dioxin-like toxicity than do dioxins and furans.[141]

Because fish constitute an identifiable source of PCBs, particularly fish eaten by sports fishermen, this population has been studied to assess PCB effects. In a study of 230 adults who ate sport fish from the Great Lakes, there were significantly lower levels of serum T4 and free T4, particularly among the 51 women in the study.[142] Both men and women had an inverse relationship between serum T4 and PCB levels, but only the men had significant associations with fish consumption and lower serum T3 levels. In a study of the Great Lakes Cohort (participants who live near and ate fish from the Great Lakes), PCB levels were significantly and inversely associated with serum levels of total T3, total T4, and TSH.[143]

In another group of fish eaters from Quebec, elevated levels of 16 PCBs were associated with lower serum T4 and higher TSH. For the women in this study the elevated levels of PCBs were significantly related to lower levels of T3.[144]

Not all studies of anglers agree, however. One study of fishermen and women in New York did not find a relationship between the 10 PCBs measured in the blood and total T4 levels.[145] A study of Swedish fishermen also found no relationship between the single congener PCB-153 and either free T4 or TSH.[136] However, these studies were constrained by the fact that Bloom et al[145] only evaluated total T4 levels and did not look at free T3, free T4, or TSH, while Rylander et al[136] only analyzed levels of a single PCB congener, PCB-153, rather than the nine congeners having been linked most strongly to thyroid disruption effects: 19, 28, 47, 118, 153, 169, 180, 183, and 187.

In studies assessing the relationship of blood PCB levels to infertility, higher levels of serum PCB levels in sub-fertile men were found to be significantly associated with lower serum T3 levels.[146]

In an area in eastern Slovakia where rivers have been highly polluted with PCBs for two decades, 2,045 adults were assessed for thyroid function related to blood PCB levels, blood DDT levels, and history of fish intake.[147] Higher blood PCB levels were associated with increased thyroid volume and higher levels of serum free T4. For those with high serum PCBs (531-1,000 ng/g lipid), there was also a positive association with serum

T3. This study also looked at TPO antibody titers and found increased frequency of TPO antibodies related to increasing levels of serum PCBs. The frequency of impaired fasting glucose (109-129 mg/dL) was also significantly higher in those with highest PCB levels.

In 335 Akwesasne Mohawk children and adolescents exposed to levels of PCBs due to local water pollution, moderate serum levels of PCBs were positively associated with TSH and inversely associated with free T4.[148] Interestingly, the relationship between higher TSH and lower T4 was stronger in those who had not been breast fed, even though the breast-fed adolescents had higher serum PCB levels, indicating a protective effect of breastfeeding.[149]

Thyroid Cancer

The incidence rates of differentiated papillary and follicular thyroid cancers have increased significantly between 1988 and 2005.[150] The incidence of papillary carcinoma between 1992-1995 and 2003-2005 increased nearly 100 percent among white non-Hispanic and black females. A lower, but still substantial increase of 20-50 percent was seen among white Hispanics, Asian/Pacific Islanders, and black males.[151] The increase, if it was due to improved detection, would most likely involve small tumors. These surveys, however, found the incidence of tumors of all sizes has increased significantly. The authors state that the evidence suggests explanations other than improved diagnoses from ultrasound and image-guided biopsy.[150]

Animal studies assessing the role of TSH in activating growth and differentiation of follicular cells have shown that a prolonged disruption of the pituitary-thyroid axis is linked to thyroid neoplasia.[152] Two mechanisms involved in the disruption of the pituitary-thyroid axis are chemically-induced blocking of thyroid peroxidase and inhibition of T4 deiodinases, which are known to occur with TD exposure.[62]

Conclusion

The Endocrine Society, in its Scientific Statement on Endocrine Disruption, refers to seven "Key Points."[1] One of them supports the "precautionary principle," suggesting it should "be used to inform decisions about exposure to, and risk from, potential endocrine disruptors." The precautionary principle, as defined by the 1998 consensus statement reads as follows: "When an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically." The statement then lists four central components that include: "taking preventive action in the face of uncertainty, shifting the burden of proof to the proponents of the activity, exploring a wide range of alternatives to possibly harmful actions, and increasing public participation in decision making."[153]

In concluding remarks at the end of the document, the authors state: "Although direct causal links between exposures to endocrine disrupting chemicals (EDC) and disease states in humans are difficult to draw, results from basic research and epidemiological studies make it clear that more screening for exposures and targeting at-risk groups is a high priority." The statement then lists recommendations for clinical practice that involve taking careful histories, including reproductive, occupational, and environmental exposure histories. The American Association of Clinical Endocrinologists recommends advising patients about avoidance and abiding by the precautionary principle to avoid exposure.

The subject of evaluating and treating background exposure of endocrine disruptors is not included in the document. NHANES data, accessible to all health care workers, measures 148 specific compounds that can be used to determine unusually high exposure levels. The document is available at www.cdc.gov/ExposureReport/pdf/thirdreport.pdf with 95th percentile levels as markers for average exposure levels.

Suggestions for appropriate and effective treatment of exposure are absent from the report. Case reports and reviews of therapeutic medical sauna protocols in adults, specifically for decreasing body burden and alleviating symptomology and pathology of PCB exposure and other fat-soluble xenobiotics have been published.[154,155] The use of dietary sucrose polyesters (olestra) in both animal models and a human case study of PCB toxicity shows total body burden may be decreased with the use of 16-20 g of olestra daily for a prolonged period. In a human case study, the period of treatment was 24 months with 16 g daily and no side effects of diarrhea or fatty stool were noted.[156-158] More research is needed to document treatment protocols that will allow for the elimination of body burdens of these endocrine disruptors.

Summary

Thyroid disease, including autoimmune thyroid disease and thyroid cancer, has a substantial incidence in the United States. The incidence of thyroid cancer is growing faster than can be explained merely by increased diagnosis as a result of better medical technology.

Thyroid disruptors consisting primarily of persistent organochlorine compounds, triclosan, phthalates and pesticides (DDT, HCB, methoxychlor, chlordane, and endosulfan) are persistent in the environment and measurable in the U.S. population.

The mechanisms for thyroid disruption have been thoroughly studied in animal populations. Human studies in both occupationally exposed and background exposed children and adults show evidence of interruption of thyroid hormone production and metabolism. Although there is no currently available way to predict the effect of a complex body burden of thyroid-disrupting chemicals in an individual patient, support in the medical literature and from medical societies suggests the need for a much more thorough evaluation of environmental exposure in the face of thyroid disease.

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