THE ROLE OF NUTRITION AND ENVIRONMENTAL TOXINS IN THYROID DISORDERS

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A thesis submitted to the Graduate Faculty of

THE UNIVERSITY OF BRIDGEPORT

In partial fulfillment of the requirements

For the degree of

MASTER OF SCIENCE

In Human Nutrition

November 27, 2011

Bridgeport, Connecticut

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Advisor

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ABSTRACT

Micronutrient deficiencies impair thyroid function. Iodine is vital to thyroid homeostasis. Both iron and vitamin A increase the efficacy of iodine supplementation. Iron supplementation improved thyroid function in iron-deficient, iron-replete adolescents. Vitamin A can reduce goiter and normalize thyroid hormones in deficient populations. Benefits of selenium are uncertain, but show promise for autoimmune thyroiditis (AIT). Mildly selenium-deficient women with AIT responded well to supplementation with significant decreases in anti-TPO antibodies. Evidence for the role of zinc is limited and inconclusive. Studies of soy isoflavones have produced conflicting results in adults given high-dose isoflavone supplements.

Environmental chemical exposures disrupt thyroid metabolism. Thyroid hormones are essential for normal neurodevelopment; therefore effects are pronounced in infancy through early childhood and in the developing fetus receiving contaminants from the mother. Phthalates and bisphenol A elevated TSH in human in several studies, but studies of their effects on other thyroid hormones are inconclusive. Many polyhalogenated compounds are structurally similar to thyroid hormones and compete for binding to thyroid hormone receptors. Individual congeners of polyhalogenated chemicals are associated with thyroid dysfunction, but more research is needed to identify others. Some polyhalogenated compounds, including perfluorocarbons and perchlorate, are strongly associated with thyroid disease, while results of polybrominated diphenylether (PBDE) and polychlorinated biphenyl (PCB) studies are inconsistent. Depressed TSH and hyperthyroidism risk was observed in studies of smokers, but the specific chemicals in cigarettes responsible have not been identified. High levels of chronic nitrate exposure may increase the risk of thyroid disease, but more studies are needed.

INTRODUCTION

Production and metabolism of thyroid hormones is highly dependent on several micronutrients. In addition, thyroid function is affected by chronic exposure to chemical contaminants that are ubiquitous in the environment.

In the normally functioning hypothalamic-pituitary-thyroid axis, when blood levels of the thyroid hormones triiodothyronine (T_3) and thyroxine (T_4) are low, the hypothalamus is stimulated to secrete thyrotropin-releasing hormone (TRH), inducing the pituitary gland to release thyroid-stimulating hormone (TSH) to stimulate synthesis of thyroid hormones. Iodine is required for the synthesis of T_4 and T_3. Thyroid follicular cells trap iodide from the blood via active transport, concentrating it to approximately thirty times the levels found in the blood. Thyroglobulin (TGB) produced in the follicular cells contains the amino acid tyrosine, which is iodinated as iodine enters the follicle. TGB binds with one or two atoms of iodine, forming monoiodotyrosine (T_1) and diiodotyrosine (T_2), respectively. A colloid forms in the follicular lumen when T_2 molecules bind with other T_2 molecules to form T_4 or with T_1 to form T_3. Once TSH stimulates the thyroid, T_3 and T_4 molecules are pinocytosed back into the follicular cells where they are cleaved from TGB and secreted in the blood to be transported by thyroxine-binding globulin (TBG). T_3 is also produced through the conversion of T_4 to T_3 by selenium-dependent deiodinases.[1, 2]

Thyroid hormones are critical for regulation of metabolism and nervous system function in humans. Fetal neurodevelopment is highly dependent upon sufficient maternal thyroid status. Maternal hypothyroidism during pregnancy and lactation can result in impaired myelination of the fetal brain and nervous system, and is the leading cause of metal retardation. This cretinism is preventable with proper replacement of iodine and other thyroid-supporting minerals in the diet.[3] Nutritional deficiencies are an enormous worldwide public health problem. Iodine deficiency is most common in low-income countries but is re-emerging in industrialized nations in part because of a trend towards low-salt diets. Many malnourished populations have concurrent deficiencies of nutrients critical to thyroid function, including iron, selenium, vitamin A and zinc, either as a result of inadequate food supply or from reliance on a plant-based diet. In addition

to cretinism, other thyroid disorders are a common result of micronutrient deficiencies, leading to goiter, hypo-and hyperthyroidism, autoimmune thyroid disorders (most notably Hashimoto's thyroiditis and Graves' disease) and a spectrum of cognitive development problems.[4] With the growing popularity of soy foods in industrialized countries, concern has arisen that the phytoestrogens in soy may have adverse effects on sex hormones and thyroid hormones.

Humans are exposed constantly to endocrine-disrupting environmental chemicals, which can also disrupt thyroid function through various mechanisms. Studies have demonstrated that the effects of these exposures have far more serious effects on fetal and infant development than on adults. Therefore, minimizing the exposure of pregnant women, babies, and young children is of utmost importance. These chemicals have been found to exert adverse effects on adult thyroid function to a lesser, yet significant, degree.

Most endocrine disruptors are classified as xenoestrogens, acting as synthetic estrogens many times more potent than the endogenous forms. They can cause more dramatic hormonal imbalances than phytoestrogens, which are far weaker than endogenous estrogens. Xenoestrogens and other contaminants have been implicated in human thyroid dysfunction. Bisphenol A (BPA) and phthalates affect thyroid receptor function. Polyhalogenated compounds inhibit the binding of thyroid hormones T_3 and T_4 to the transport proteins transthyretin (TTR), thyroid binding globulin (TBG), and albumin. Some of the most studied polyhalogenated chemicals are the organochlorines (including polychlorinated biphenyls or PCBs; dioxins, and pesticides such as DDT); Perfluorocarbons (most notably, perfluorooctanoic acid or PFOA; and perfluorooctane sulfonate or PFOS); and perchlorate. Perchlorate and nitrate have been shown to compete with iodine for uptake by the sodium-iodine symporters (NIS) in thyrocytes. Cigarette smoke contains hundreds of known endocrine disruptors, toxicants and carcinogens. One of these compounds, thiocyanate, is also known to be a NIS competitor, but much more research is needed to isolate the cigarette compounds responsible for observed thyroid suppressive effects.[5, 6]

Nutrients that affect thyroid function

Iodine

Iodine is crucial for the manufacture of thyroid hormones. The recommended intake of iodine is 90 mcg/day for children, 150 mcg/day for adults, and 220 mcg/day for pregnant and lactating women.[7] According to estimates by the World Health Organization (WHO), about one-third of humanity in 2007 was iodine deficient.[8] Iodine deficiency in adults is associated with primary hypothyroidism, goiter and thyroid cancer. Fetal neurological development suffers with iodine deficiency of the mother; neuropsychological development in infants and children is dependent on the iodine status of the breast-feeding mother and of the overall iodine intake in the child's diet. Mild maternal deficiency often results in lower intelligence and learning deficits in children. Moderate to severe deficiency can cause brain damage, hearing loss, and cretinism.[4]

While iodine insufficiency is often viewed as a third-world issue, many landlocked countries and regions worldwide share this problem. Iodine occurs naturally in coastal soils and is abundant in seafood, especially seaweed. Inland areas lack iodine in their soils, resulting in iodine-deficient crops and food animals, making iodine supplementation necessary to prevent goiter and hypothyroidism. A substantial portion of the population of the United States is iodine deficient. The 2007-2008 NHANES survey showed the prevalence of iodine insufficiency (defined as urinary iodine < 100 mcg/L) in the U.S. to be 28.2% +/- 1.1%.[9] One reason for the decline in iodine status in developed countries is the medical advice in recent decade to lower salt intake to prevent hypertension. By contrast, populations in Japan have long consumed large amounts of iodine in their diet, mostly as seafood and seaweed, with low prevalence of autoimmune thyroiditis and iodine-deficiency goiter.[3, 10] The Japanese diet has much higher levels of iodine than most of the world, primarily as a result of using seaweed as a dietary staple. Seaweed concentrates iodine from seawater, retaining it in high concentrations much as human thyroid tissues does. Various studies estimate Japanese daily iodine intake from seaweed to be as high as 50 mg/day, which is 15 times the safe upper limit defined by the Ministry of Health, Labor and Welfare of Japan, and over 40 times the tolerable upper intake level as set by the Institute of Medicine (IOM). Coastal populations may approach

these numbers, but a more realistic number for iodine consumption may still be as high as 3 mg daily.[11]

Iodine deficiency has been extensively studied in moderately to severely iodine-deficient populations. Many studies of such people warn against supplementing with iodine in excess of the IOM recommendation of 150 mcg/day. Pharmacologic doses intended to treat hypothyroidism can lead to goiter and hyperthyroid or autoimmune thyroid conditions. However, differences in tolerance for larger iodine doses in iodine-deficient regions versus those that have long been iodine sufficient have been observed. In populations with concurrent iodine and selenium deficiencies, treatment with iodine alone has been known to increase risk of thyrotoxicosis in a few studies, but overall evidence is inconclusive regarding this effect. Iodine supplementation in iron-deficient communities, on the other hand, has been found in several studies to be ineffective if not accompanied by iron supplements.[4, 12]

Iron

Iron deficiency has been found to impair thyroid hormone synthesis. Thyroperoxidase (TPO) is necessary for the oxidation of iodide to iodine, allowing the organification of iodine to synthesize thyroid hormones. TPO is a heme-dependent enzyme; therefore, iron deficiency reduces TPO activity and interferes with thyroid hormone production, even in iodine-replete individuals. In iodine-deficient populations with coexisting iron deficiency, iodine supplementation is significantly more effective with concurrent iron supplementation than when given independently.[13]

Selenium

Similarly to iodine, selenium is deficient in the soil and food supply of many regions of the world. In late fetal and early neonatal development, severe deficiency of iodine and selenium together can result in myxedematous cretinism and Kashin-Beck disease. In some regions of China, selenium deficiency without accompanying iodine

deficiency can increase susceptibility to Keshan disease as a result of infection with the Coxsackie B virus. Much as it does with iodine, the thyroid gland conserves selenium when body levels are inadequate. Selenium is essential to the structure of selenoproteins required for thyroid hormone synthesis and metabolism, including glutathione peroxidase (GPx), the deiodinases, and thioredoxine reductases. Selenium also protects the thyroid when iodine is in excess. However, some studies have shown that in moderately to severely iodine-deficient populations with concurrent selenium deficiency, the risk of developing hypothyroidism may be increased if selenium is administered before iodine status is corrected.[13]

In adults, selenium deficiency can lead to development of autoimmune thyroiditis. GPx is necessary to reduce the hydrogen peroxide (H_2O_2) produced during the oxidation of iodide. Animal models have shown that excess H_2O_2 will oxidize TPO, causing the production of anti-TPO antibodies (TPOAb) and autoimmune thyroiditis.[14] Three small recent human studies on adults confirmed that selenomethionine supplementation in autoimmune thyroiditis patients resulted in significant reduction of TPOAb.[15, 16, 17] A similar randomized controlled trial of children and adolescents found that supplementation with sodium selenite did not decrease TPOAb.[18]

Vitamin A

Vitamin A has been found to increase iodine efficacy in children deficient in both nutrients. Vitamin A deficiency causes goiter, impairs iodine uptake by the thyroid, and interferes with thyroglobulin production and with the binding of the iodotyrosines T_1 and T_2 to form the thyroid hormones T_3 and T_4. Deficiency in vitamin A also decreases the conversion of T_4 to T_3 in hepatocytes. In addition, it decreases T_3 uptake, resulting in increased free T_3 and T_4. Few well-designed human studies on the interactions of vitamin A and iodine in humans exist, thus further research will be needed to better understand this relationship.[4]

Zinc

As with vitamin A, few human studies regarding the role of zinc in thyroid health have been undertaken. About 100 human metabolic enzymes are zinc-dependent, but it is not known if zinc plays a role in synthesis or metabolism of thyroid hormones in humans. Populations dependent on diets low in animal products are at risk for zinc deficiency. No conclusive evidence for an association between zinc deficiency and human thyroid function has been found.[4]

Soy isoflavones

Despite long-known thyroidal effects of feeding soy formula to infants, studies have not found a significant effect on thyroid function in adults eating a diet high in soy isoflavones. Study methods varied, however. Some studied whole soy preparations, and others isolated single phytoestrogens in unnaturally high doses. More study is needed on soy at levels found in normal diets.[19]

Environmental toxins that affect thyroid function

Phthalates and bisphenol A (BPA)

Phthalates are added to plastics to increase pliability, and is found in toys, food packaging, adhesives, pharmaceuticals (in timed-release coatings), and blood bags and medical tubing. They are also used as an ingredient in cosmetics and perfumes, and as solvents in other personal care products such as lotions.[20, 21] BPA is a component of polycarbonate plastics and has been used since the 1960s in hard plastic bottles and in the lining of food and beverage cans. It is ubiquitous in household products and can be found in items such as baby bottles, eyeglass lenses, dental composites, floorings, some paints, epoxy resins, and plastic dinnerware. According to the CDC, 5 to 6 billion pounds of bisphenol are produced each year.[22]

Exposure of patients to phthalate and BPA contamination from plastic hospital equipment has been of concern for doctors and hospital staff. A French epidemiological study assessed exposure of 250 pregnant women to phthalates and bisphenol A suggests that the women were exposed to high levels of these chemicals while in the hospital via standard medical equipment such as catheters and IV tubes. Supporting this finding is the significantly higher urinary concentrations of free BPA found in women who delivered by cesarean section. Further study is needed both on larger populations of women but also on newborns, who also face potential exposure to phthalate and BPA in the hospital, for example during catheterization or IV feeding.[23]

Polyhalogenated compounds

The molecular structures of polyhalogenated compounds such as brominated flame retardants, such as polybrominated diphenylethers (PBDE), polychlorinated biphenyls (PCBs), and their metabolites, are similar to the structures of thyroid hormones. These chemicals may therefore directly displace thyroid hormones, disrupting their function. Polyhalogenated compounds are lipophilic and bioaccumulate up the food chain, concentrating in adipose tissue and in milk.[24] Results of human studies are mixed: some congeners are linked to thyroid dysfunction while others show insignificant effects.

Polybrominated diphenylethers (PBDE)

PBDEs are used in flame-retardant materials, including children's clothing, furniture, and electronics. Very few human studies have examined the association between PBDEs and thyroid function. No significant effects on thyroid function in young children exposed to PBDEs were found, nor were effects seen in children with known maternal exposure to PBDEs. PBDEs were observed to lower TSH levels in pregnant women, but the study did not follow up on possible effects of low maternal TSH on their children. It should be noted that European studies have found significantly lower levels of PBDE exposure than in North America. Several studies have shown that the

U.S. population is contaminated with a higher level of all polyhalogenated compounds than are Europeans.[25, 26, 27]

Organochlorines

Organochlorines (OCs) are used in a wide variety of products. Organochlorine pesticides include dichlorodiphenyltrichloroethane (DDT), which was banned in the U.S. in 1972 and worldwide in 2001 for use on food crops, but is still permitted for malaria control. DDT and its metabolites persist in the environment and in humans worldwide. In the U.S. almost all people continue to have detectable levels of *p,p'*-DDE (a DDT metabolite) in their serum.[28] There are few human studies on the effects of OCs on human thyroid function and development. OCs are known to depress thyroid hormone concentrations in adults and children. As with all polyhalogenated compounds, OCs have a similar structure to thyroid hormones and may bind to transport proteins, displacing T_3 and T_4 and stimulating TSH.[29]

Polychlorinated biphenyls

Polychlorinated biphenyls (PCBs) were produced in the U.S. from 1929 to 1979. PCBs were used in plasticizers; pigments and dyes; carbonless copy paper; adhesives; thermal insulation; hydraulic fluid; and electrical transformers among other applications. Its production was banned in the U.S. in 1979, but PCBs persist in the environment and in plants, fish, and humans.[30] PCBs are present in most humans living in industrialized countries. Most PCB congeners are xenoestrogens, and their hydroxylated metabolites are even more potent estrogen imitators. The half-life of PCBs varies by congener and by individual metabolism, with half-lives ranging from 3 to 17 years. PCBs are carcinogenic and disrupt thyroid function as well as most other organ systems. As polyhalogenated chemicals, PCBs are chemically similar to thyroid hormones and have been found to inhibit thyroid function in human studies.[31]

Perfluorocarbons

Perfluorooctanoic acid (PFOA) is a component of stain-resistant carpets and fabrics, water-resistant clothing (Gore-Tex), microwave popcorn bags and other food packaging, and nonstick cookware (Teflon). Perfluorooctane sulfonate (PFOS) was used in Scotchgard and other stain repellents, cleaning products, and semiconductors.[32]

PFOA and PFOS differ from other persistent organic pollutants (POP). While most POPs accumulate in adipose tissue, PFOA and PFOS instead bind to serum proteins. The kidneys do not process these compounds. As a result, PFOS has a half-life of 3.8 years in the human body, and PFOA 5.4 years. Animal studies have shown that PFOS and PFOA affect thyroid function and suggest several different mechanisms.[33]

Perchlorate

A small amount of perchlorate occurs naturally in soil. Larger amounts of perchlorate contamination in water and soil occur as a byproduct of the production and use of solid rocket fuels, road flares, and explosives. Many water sources and food crops (particularly green leafy vegetables) across the United States are contaminated with perchlorate. Perchlorate is a potent competitor of iodine for uptake by sodium-iodide symporters (NIS) in the thyroid gland.[34]

Cigarette smoke

Cigarette smoke contains over 200 known toxicants and endocrine disruptors.[35] Cigarette smoke has been shown to inhibit thyroid hormone function, and one of the primary chemical components of cigarettes thought to be responsible for this effect is cyanide. Cyanide in cigarette smoke is metabolized to yield thiocyanate. Like perchlorate, thiocyanate is a NIS competitor, but is approximately 15 times weaker than perchlorate.[5]

Nitrates

Nitrates are a common drinking water contaminant, especially in agricultural areas where nitrogen fertilizers are used. Green leafy vegetables and some root vegetables contain some nitrates, with higher levels found in conventional produce than in organic. Nitrates bind to NIS on thyroid follicle cells, inhibiting iodine uptake, interfering with the manufacture of T_3 and T_4 and increasing TSH.[36]

LITERATURE REVIEW

Nutrients that affect thyroid function

Iodine

A cohort study in China, which investigated the effects of iodine supplementation in previously mildly deficient people, found that iodine supplementation in the mildly deficient may not increase the incidence of hypothyroidism. 3108 residents of three rural Chinese communities were studies over five years. Participating communities were mildly iodine deficient, iodine sufficient (but previously mildly deficient), and in iodine excess. Median iodine excretion was 88 mcg/L, 214 mcg/L, and 634 mcg/L, respectively. Thyroid ultrasound was performed and measurements of thyroid hormones and antibodies taken. Incidence of hyperthyroidism was 1.4% in the mildly deficient group, 0.9% in the sufficient group, and 0.8% in the excessive iodine group. Autoimmune hyperthyroidism was prevalent in all three groups. Chronic iodine excess was not found to increase the incidence of autoimmune hyperthyroidism, suggesting other factors than iodine are key to the occurrence of this condition.[37]

In a similar study of a previously severely iodine deficient population in China, goiter was found to be significantly reduced in primary school children, while IQ scores showed little improvement. In each of 30 primary schools in the region, 40 children, ages 8-10, underwent thyroid examination and IQ testing. Of each set of 40 children, 12 were evaluated for urinary iodine excretion levels. The same measurements were made in 1995 and repeated in 2005 with a new cohort of 8-to-10 year olds. The goiter rate fell

from 38.7% to 13.5% over the decade, and median urinary iodine excretion, a measure of iodine repletion, increased from 119.9 mcg/L to 191.8 mcg/L. Neurodevelopment appeared to still be adversely affected, however: IQ scores improved only slightly, from 91.0 to 96.9. Other nutrients were not measured in this study. It would be important to know the iron and selenium status of this population for future comparison with other similar iodine supplementation programs.[38]

Selenium

In addition to iodine, selenium is key to maintaining thyroid homeostasis. Thyroid disease is common in iodine-sufficient regions as well as in iodine-deficient areas, so more human studies elucidating the effect of selenium and other nutrients on thyroid health are necessary.

A cross-sectional study within a randomized, double blind, placebo-controlled trial of French adults found a gender disparity in the effects of selenium supplementation on thyroid function. The SU.VI.MAX study examined the effectiveness of daily supplementation of vitamins and minerals for the prevention of various chronic health problems. Participants were examined at baseline in 1994 and monitored for eight years. One year into the trial, a random subset of subjects was selected for a cross-sectional study on the effects of selenium levels on thyroid volume. 1900 volunteers (792 men aged 45-60 and 1108 women aged 35-60) were chosen for evaluation of thyroid volume, serum TSH, free T_4, selenium, retinol, beta-carotene, alpha-tocopherol, and urinary iodine and thiocyanate. Exclusion criteria included: high urinary iodine and thiocyanate excretion; on thyroid hormone treatment, anti-thyroid medications, or lithium; or had undergone thyroid surgery. Confounding factors included age, gender, menopausal status, hormonal status, BMI, and history of smoking and alcohol consumption. The type of selenium given to subjects was not specified. In women, selenium significantly lowered the risk of increased thyroid volume and goiter. In men, the association between thyroid volume and selenium was statistically insignificant.[39]

A randomized, double blind, placebo-controlled trial of older New Zealanders found that twelve weeks of selenium and iodine supplementation did not significantly influence thyroid function. One hundred subjects, aged 60-80 years, were divided into four groups to received one tablet daily of 100 mcg of selenomethionine; 100 mcg selenomethionine plus 80 mcg of iodine (as potassium iodate); 80 mcg of iodine; or placebo. Measurements were taken of TSH, Tg, urinary iodine, plasma selenium, whole blood GPx activity, and BMI. Participants were moderately iodine deficient (median urinary iodine concentration 48 mcg/L); by the end of the study they were still mildly iodine deficient (UIC < 100 mcg/L). In response to supplementation, the selenium group did not have a significant change in thyroid function. TSH, free T_4, and thyroglobulin concentrations were unchanged at the end of the study, and free T_3 changed insignificantly ($P = 0.080$). This study was small and of short duration, yet it suggests that selenium status of participants at baseline was not low enough to disturb thyroid function and production of selenoenzymes.[40]

A long-term clinical trial investigating the effects of long-term selenomethionine supplementation on thyroid hormones in adults found a statistically significant increase of 5% per year in T_3 concentrations in men. This finding may be clinically insignificant, however, because there was no concurrent change in TSH concentration. Twenty-eight participants (13 men, 15 women) were given 200 mcg of selenomethionine per day for 28 months. Plasma selenium, T_3, T_4, and TSH were measure at baseline and then every three months for the duration of the trial. No clinically significant effects were observed in thyroid hormone concentrations after adjustment for age, BMI, and seasonal effects on hormone concentrations. While the authors were careful to adjust for confounders, even ensuring that blood samples were drawn on in the morning to account for diurnal fluctuations in TSH, this study was too underpowered to be of clinical use. Larger long-term supplementation trials are necessary, and these should include measurements of complementary nutrients including selenium and iron at a minimum.[41]

A small randomized, controlled prospective study investigating the effects of 6 months of selenomethionine supplementation on patients with Hashimoto's thyroiditis observed that TPOAb concentrations decreased significantly as compared with placebo.

Sixty-five adults (56 female, 9 male) with autoimmune thyroiditis (AIT) were evaluated at baseline for serum TPOAb, anti-thyroglobulin antibodies (TgAb), TSH, T_3 and free T_4. Participants were divided into two groups: group 1 (n = 34) was administered L-thyroxine (LT_4) plus 200 mcg/day of selenomethionine, and group 2 (n = 31) received LT_4 and placebo. At baseline, mean serum levels of selenium were 75 +/- 6 mcg/L, within the normal reference range of 70-125 mcg/L. After 3 months, mean TPOAb in the placebo group decreased 21% and 27% at 3 months and 6 months, respectively ($P < 0.0005$). In the selenomethionine group, TPOAb concentrations decreased 46%; decreasing further after 6 months to 55.5% ($P < 0.0001$). There were no statistically significant changes in either group for any of the other serum markers measured. Future studies would benefit from larger sample size and equal numbers of males and females to examine and gender difference in the effects of selenomethionine supplementation on the thyroid.[15]

Another study of AIT patients showed that long-term therapy with 200 mcg/day of selenomethionine was effective in lowering TPOAb levels in adult women with AIT, while 100 mcg/day of selenomethionine proved to be ineffective. This randomized controlled trial examined 88 women (mean age 40) given L-thyroxine (LT_4) plus placebo (group C; n=40) or LT_4 and 200 mcg selenomethionine daily (group S2; n=48) for 3 months. After 3 months, the placebo group showed a statistically insignificant increase in mean TPOAb, going from 770.3 IU/ml to 773.4 IU/ml ($P > 0.05$). The selenomethionine-supplemented group saw a significant decrease in mean TPOAb levels, beginning at 803.9 IU/ml and decreasing 26.2% to 572.3 IU/ml ($P < 0.001$). After the first 90 days, the study continued with 40 participants from the selenomethionine group, randomizing subjects into group S21 and group S22. S21 (n = 20) continued selenomethionine supplementation at 200 mcg while S22 received a reduced dose of 100 mcg (n=20). Mean serum TPOAb concentration in the 200-mcg group decreased significantly, from 649.2 IU/ml to 443.2 IU/ml ($P < 0.01$). For group S22, mean TPOAb levels significantly increased from 544.3 to 694.9 IU/ml ($P < 0.01$). Six months into the study, the participant pool shrank further; reasons for the attrition at three and six months were not given. Twelve of the women in group S22 (group S222) continued to take the 200-mcg selenomethionine supplement daily. A subset of twelve women from the S21 group (group S212) resumed a daily selenomethionine dose of 200 mcg after having

taken 100 mcg/day for the previous three months. At baseline and at the end of each 90-day study phase, serum measurements were taken for TPOAb, thyroglobulin antibody (TgAb), TSH, free T_3 and free T_4. Apart from the TPOAb values discussed previously, no statistically significant changes of these parameters was found in any group. This was an underpowered and poorly designed study, but yielded promising results, which need to be investigated further with a much larger sample of AIT patients.[16]

Another small trial, a randomized, single-blinded, placebo-controlled prospective study examining the association between selenium supplementation and TPOAb in adult women, found similar results with sodium selenite. Seventy women (mean age, 47.5 years) with AIT and TPOAb and/or TgAb concentrations > 350 IU/ml were selected and randomized into two groups matched for age and TPOAb levels. All participants received levothyroxine to normalize TSH. Thirty-six subjects were given 200 mcg/day of sodium selenite; thirty-four took placebo. Serum TSH, free T_3, free T_4, TPOAb, and TgAb were measured along with thyroid ultrasound. TPOAb decreased 36.4% (P = 0.013) in the selenium group compared with 22% (P = 0.95) in the placebo group. Ultrasound echogenicity of the thyroid improved in nine of the selenium-treated subjects versus only two women in the placebo group; these same subjects also showed normalized TPOAb concentrations at the end of the study. TgAb levels significantly decreased in the placebo group, while the selenium group showed no change in TgAb. As with the other selenium studies, more research with larger groups and more refined analysis are needed to determine the real efficacy of selenium for AIT and other thyroid conditions.[17]

The only study of the effects of selenium on AIT in children and adolescents, by contrast, found that supplementation with 200 mcg/day of sodium selenite did not decrease TPOAb. This randomized, non-blinded prospective study examined 49 young participants (mean age 12.2 years) diagnosed with AIT, but no other autoimmune diseases. They were randomized into three groups. During the 12-month study, group A received levothyroxine alone (n = 18); group B was given levothyroxine with 100 mcg of sodium selenite per day (n = 13), and group C received levothyroxine with 200 mcg/day of sodium selenite (n = 18). Subjects were not taking other medications, such as anti-

inflammatories or immunosuppressants. Sample and data collection procedures were identical for every patient. In contrast to similar studies on adults, no statistically significant decrease in TPOAb levels was found at the end of the study, but groups A and C both showed statistically significant decreases in thyroglobulin antibodies (TgAb). The authors note that there is no known physiologic interaction between selenium and thyroglobulin, so the observed effect may be a result of levothyroxine treatment rather than of sodium selenite supplementation. In addition, since TgAb is not thyroid-specific, this may not be a clinically significant finding. More research is needed to discover whether children and adolescents respond differently to selenium supplementation or whether sodium selenite is an ineffective form of supplementation for AIT treatment.[18]

Iron

A recent case-control study in India found that in this iodine-sufficient area, a high prevalence of goiter persisted, as a result of iron deficiency. This study compared 191 goitrous children with 165 non-goitrous children in a previously iodine-deficient area examined the effects of iron and selenium status on the incidence of thyroid autoimmunity. All participants were evaluated for urinary iodine concentration, serum TPOAb, T_3, T_4, TSH, selenium, hemoglobin, and ferritin. Serum selenium levels and urinary iodine concentrations were similar and sufficient in both groups. Of the goitrous children, 37.4% were anemic compared with 24.8% of the non-goitrous group. Fewer participants in the control group were iron-depleted (6.4%) than in the goitrous group (20.6%) ($P = 0.001$). The odds ratio of low serum ferritin associated with goiter was found to be 2.8 ($P = 0.017$). This strong correlation between iron status and goiter in iodine-replete children should be more closely examined and public health programs modified to account for populations' iron status when distributing iodine fortification.[42]

A randomized, double blind, placebo-controlled trial of iron-deficient adolescent girls in Iran found that thyroid function is significantly altered by iron deficiency. 431 participants were divided at random into two groups. Over 12 weeks, one group was given 300 mg ferrous sulfate tablets orally, 5 times per week; the other group received an

identical-looking placebo. Baseline and 12-week serum measurements were taken of hemoglobin; hematocrit; albumin; total iron binding capacity (TIBC); iron; ferritin; total and free T_3 and T_4; resin T_3 uptake; and reverse T_3. No evaluation of iodine status was conducted, but at baseline, all subjects were found to have normal thyroid function and depleted iron stores. At 12 weeks, hemoglobin and iron improved significantly in both groups; the authors propose that better availability of citrus fruits at the time of year the study concluded enhanced iron absorption as a result of higher vitamin C intake. In the iron supplementation group, iron deficiency was corrected and serum concentrations significantly increased for total T_4 (+16%), total T_3 (+9%) and resin T_3 uptake (+11%). Compared with the placebo group, these changes were statistically significant. Free T_4 levels increased but this increase was not significant compared with the placebo group. Reverse T_3 concentrations showed a 50% decrease in comparison with the control group. Changes in TSH and free T_3 did not change significantly in either group.[43]

A similar smaller study also found that iron supplementation improves thyroid function in adolescent girls who are sufficient in both iodine and selenium. In such a population, iodine alone was ineffective in normalizing thyroid function. This 12-week, randomized, double blind intervention study followed 103 iron-deficient but non-anemic 14-to-18-year-old girls to investigate the effects of iodine and iron supplementation on their thyroid function. All participants started the study in an iodine- and selenium-replete state. The 94 girls that completed the study were in four groups: one group (*n*=24) received a one-time dose of 190 mg of iodine and 300 mg of ferrous sulfate (60 mg of elemental iron) 5 times per week; the second group (*n*=23) was given ferrous sulfate only; a third group (*n*=25) received iodine only; while the last group (*n*=22) received placebo. Hemoglobin, ferritin and transferrin saturation increased significantly in both the iron + iodine group and the iron group. Some thyroid hormone levels improved with improvement of iron status. Compared with the iodine and placebo groups, both iron-supplemented groups showed significant increases in total T_4 and T_3, and resin T_3 uptake, while reverse T_3 declined considerably. Changes in TSH were not significantly different among the four groups. Iron supplementation was found to improve thyroid function on its own; co-supplementation of iron with iodine was not observed to enhance the effects of iodine.[44]

In an iodine- and iron-deficient population of children with a high rate of anemia, it was found that iodine supplementation, in the form of iodized salt, was more effective when microencapsulated iron was added. In this 9-month randomized, double blind, controlled trial of 377 children in Morocco, ages 6 to 15, were given either iodized salt or salt fortified with iodine and iron (as ferrous sulfate). After 40 weeks, decrease in thyroid volume was 38% in the iodine plus iron group, compared with an 18% decrease in the iodine group. Additionally, serum thyroxine and goiter levels both decreased significantly in the dual-fortified group. These findings suggest that iodine supplementation is relatively ineffective in populations who are iron-deficient.[45]

In Cote d'Ivoire, a significant decrease in goiter prevalence was found in iron-deficient children with goiter, supplemented with both iron and iodine as compared with those given iodine only. 166 goitrous, iron-deficient children in participated in a 20-week randomized, double blind, placebo-controlled trial to determine whether iron supplementation would improve the efficacy of iodine supplied in iodized salt. After 20 weeks, in addition to significant improvement of hemoglobin and iron status, mean thyroid size reduction in the placebo group was approximately half that experienced in the iron-treated group. No significant differences in thyrotropin (TSH) or thyroxine (T_4) were observed between groups either at baseline or afterwards. At the conclusion of the study, goiter prevalence in the iron-supplemented group dropped to 19% below that of the placebo group: 43% and 62%, respectively.[46]

Vitamin A

Vitamin A has been found to increase iodine efficacy in children deficient in both nutrients. In this double blind, randomized, 10-month trial, 138 children in Morocco with both moderate vitamin A deficiency and iodine deficiency disorders were given iodized salt and either 200,000 IU of vitamin A or a placebo. At baseline, 5 months and 10 months, thyroid function and vitamin A status were evaluated. In the 136 children completing the study, goiter rate, median TSH, and mean thyroglobulin were all significantly decreased in the vitamin A group compared with the placebo group.[47]

A more recent study by Zimmerman, et al., also tested the effects of vitamin A supplementation compared with iodine supplementation and vitamin A plus iodine. The 6-month randomized, double blind, intervention trial followed 404 children in South Africa. At baseline, the majority of participants were mildly iodine-deficient: 31% were moderately deficient and 27% had goiter. Thyroid hormones were in the normal range for most of the subjects. At months 0 and 3, one group was given 191 mg of iodine (as iodized oil) plus placebo; the second group received the same iodine treatment plus 200,000 IU of vitamin A (as retinyl palmitate); the third group was administered both iodine and vitamin A; and the fourth group received placebo. Urinary iodine, thyroid volume, TSH, total T_4, thyroglobulin, serum retinol and retinol-binding protein were measured at baseline, at 3 months, and at 6 months. Vitamin A deficiency was not found to inhibit the efficacy of iodine supplementation, but the data suggest that in cases of iodine sufficiency, high doses of vitamin A likely have no effect on thyroid function. Vitamin A supplementation was found to decrease excess TSH production, reducing risk of goiter. Serum thyroglobulin also decreased with vitamin A treatment, but T_3 and T_4 concentrations were not significantly affected. No significant interactions were discovered between iodine and vitamin A in effects on urinary iodine concentrations, serum retinol or retinol binding protein.[49]

Zinc

A cross-sectional, placebo-controlled study in Pakistan found that zinc supplementation in goitrous adults improved serum thyroid hormone levels along with zinc status. Of 352 volunteers, aged 16-30 years, 132 (60 male, 72 female) were treated with 30 mg of zinc for 6 months. The form of zinc used in this study was not specified. 220 Age-matched controls without goiter received placebo. Exclusion criteria were: mineral supplementation during previous 3 months; hypertension; smoking; diabetes; alcoholism; use of any antioxidant vitamins or minerals; cardiovascular disease. Serum and urinary zinc were measured. At baseline, serum zinc was significantly lower and urinary zinc excretion significantly higher in goitrous subjects than in controls. TSH was significantly higher, and free T_3 and free T_4 significantly lower in goitrous male and

female participants. After 6 months of treatment, serum zinc concentration increased and urinary zinc fell, indicating absorption of the zinc supplement and improvement of zinc status. Concurrently, TSH levels in goitrous men and women fell. More significantly, free T_3 and T_4 concentrations after treatment rose above those of controls after zinc supplementation.[49]

By contrast, a cross-sectional study of schoolchildren in Iran found that zinc deficiency does not affect the prevalence of goiter. Urinary iodine concentrations (median 195.5 mcg) reflected iodine sufficiency. Serum zinc levels in 94 goitrous and 326 non-goitrous children did not show a significant difference in zinc deficiency between these groups. As we saw in other studies of Iranian schoolchildren, other deficiencies, most notably iron, also have significant effects on thyroid function. This confounder was not accounted for in this study.[51]

Soy isoflavones

Intake of the phytoestrogen genistein was not found to be associated with a significant additional risk of subclinical or clinical hypothyroidism in 77 participants. Selected from a larger randomized, double blind, placebo-controlled trial of postmenopausal women with osteopenia, 389 women were given either 54 mg or genistein aglycone or placebo daily for 24 months; a sub-cohort of these women continued the genistein therapy for 12 additional months (71 received genistein, 67 placebo). In addition, both groups were given vitamin D_3 (400 IU) and calcium (500 mg). 40 genistein and 37 placebo subjects completed the full study. After 3 years, free T_3 levels declined slightly in both groups, but these were in a normal range defined as 1.80-4.60 pg/ml. The isolated form of phytoestrogen, genistein aglycone, is only a small fraction of what occurs in soy foods. Further studies are needed to evaluate other isoflavones as present in soy foods.[51]

A more recent study, however, found that in subjects with subclinical hypothyroidism, supplementation with 16 mg of soy phytoestrogens daily for 8 weeks tripled their risk for developing clinical hypothyroidism. This randomized, double blind,

crossover study divided 60 subjects (52 female, 8 male) with subclinical hypothyroidism, aged 44-70 years, into two groups, receiving either a high dose of phytoestrogens (30 g of soy protein with 16 mg of phytoestrogens) or a low dose (30 g soy protein with 2 mg of phytoestrogens). Supplements were taken daily for 8 weeks. After an 8-week washout period, the groups crossed over for another 8-weeks of supplementation. All participants were iodine-sufficient. Levels of phytoestrogens at baseline and after the washout period were similar in both groups. The phytoestrogen preparation consisted of 54% genistein, 35% daidzein, and 12% glycitein. Six female participants (10%) developed overt hypothyroidism (TSH > 4.7 mU/L and free T_4 < 9 pmol/L) after supplementation with 16 mg of phytoestrogens daily; three had received the low-dose supplement first, while an equal number received the reverse protocol. Only one of the six tested positive for TPOAb. With only 8 males in this underpowered study, the risk of hypothyroidism in response to high phytoestrogen intake in males could not be determined.[52]

No adverse thyroid effects and no statistically significant difference in TSH, T_3 and T_4 concentrations was found with a daily intake of 90 mg of soy aglycones in a study of postmenopausal women. This randomized, double blind, placebo-controlled study evaluated 38 postmenopausal volunteers, aged 64-83 years and not undergoing hormone replacement therapy (HRT). All were evaluated at baseline, 3 months and 6 months for serum TSH, T_3 and T_4. Iodine status was not measured; however, all subjects were given a multivitamin and multimineral supplement that included 150 mcg of iodine. Some of the women were taking thyroid medication and some were smokers; there were the same number of such subjects in each group. Participants were randomized into an isoflavone-supplemented group and a placebo group. The isoflavone-supplemented group was given 90 mg of isoflavones (genistein, daidzin, and glycitin, in a 1.3:1.0:0.3 ratio) daily. This is the equivalent of approximately 9 to 12 ounces of tofu, noted by the authors to be roughly two to three times the average Japanese intake for adults. After six months this study found no statistically significant difference in thyroid hormone concentrations within each group. Neither was there any significant difference found between the isoflavone group and the control group at the end of the study. We do not know if any of the subjects were iodine, iron or selenium deficient at the start of the trial,

making the addition of the multivitamin with iodine a confounding factor for which was not compensated for in the statistical analysis.[53]

A 12-week randomized, double blind, placebo-controlled trial observed a significant decrease in serum free T_3 concentrations in oophorectomised women ingesting 75 g of isoflavones daily (25% genistein and genistein, and 15% daidzein and daidzin) daily while the other was given placebo ($n = 22$). Of the 43 women entering the study, 34 completed it. Statistical analysis was done on an intention to treat principle. Isoflavones were not found to have a significant effect on thyroid hormones or thyroid antibodies aside from free T_3.[54]

Environmental toxins that affect thyroid function

Phthalates and bisphenol A

A recent cross-sectional analysis of NHANES 2007-2008 data from 1,346 adults and 329 adolescents found that effects of phthalate and BPA exposure varied between these age groups. Increasing phthalate exposure was associated with decreasing total T_4 in serum in adults. Increased urinary BPA also significantly decreased serum T_4 concentrations in adult subjects. The study identified an inverse relationship between urinary metabolites of DEHP [di(2-ethylhexyl) phthalate] and thyroid hormones and thyroglobulin, but a positive association with TSH, suggesting a direct effect on thyroid function. Adolescents exhibited a different response, showing a significant increase in total T_3 and TSH with increasing DEHP metabolite levels with negligible changes in T_4 concentration.[55]

A cross-sectional study of 76 pregnant women in Taiwan tested for thyroid hormone concentrations in serum and the presence of five phthalate biomarkers in urine during the second trimester of pregnancy. In addition to biomarker testing, an interview questionnaire provided information about personal history, lifestyle factors (tobacco and/or alcohol use) and potential sources of phthalate exposure. Participants were asked if they had moved to a new house or workplace during the previous year, if any

remodeling or painting was done at home or workplace, and if any medical care was received during the previous three months (blood transfusion, IV drip, oxygen mask) which could result in higher than average exposure to phthalates. Of these five bioesters, monobutyl phthalate (MBP) was found to have an inverse relationship with T_4 and free T_4 serum concentrations. Obviously, this study was rather limited due to its small size. In addition, only one urine sample and one serum sample were used; multiple readings over a larger time span would improve reliability of measurements. As these authors note, plastic laboratory equipment is a potential confounder because it may add to the phthalate contamination of the samples.[56]

Polybrominated diphenylethers

Polybrominated diphenylether (PBDE) exposure was found to be associated with lower maternal TSH levels in a recent cross-sectional study of pregnant women. 270 women, in approximately the 27th week of pregnancy, were evaluated for levels of free T_4, total T_4, TSH, and 10 specific PBDE congeners. Five of the congeners were detected in > 50% of samples; the other five were not detected in the majority of samples and were excluded from further analysis. PBDE congeners 28, 47, 99, 100 and 153 were found to have an inverse relationship with TSH, but no statistically significant association with T_4. Higher levels of overall PBDEs and specifically of PBDEs 100 and 153 were associated with increased risk of subclinical hyperthyroidism. Many confounders were accounted for, including socioeconomic factors and exposure to other environmental endocrine disruptors such as PCBs, lead, and OCPs.[27]

A prospective birth cohort study in Spain investigated pre- and post-natal PBDE exposure through age four in a group of children. PBDE had no apparent effect on concentrations of TSH and free T_4; total T_3 showed a positive but statistically insignificant correlation with serum levels of PBDE 47. PBDE concentrations were measured in cord blood of 88 babies and in serum of 244 four-year-olds. At age 4, levels of TSH, free T_4 and total T_3 were measured. Because only 49 children had PBDE measured in both cord blood at birth and serum at age 4, separate analyses were

performed on these two sets of data. This was an underpowered study that relied heavily on statistical imputations to fill in for missing data. As a result, these results are not reliable.[26]

A multi-center cohort study of mothers and newborns in Norway examined the associations between measured levels of brominated flame retardant (BFR) chemicals in maternal breast milk and TSH concentration in the babies. Milk samples from 396 mothers were analyzed for hexabromocyclododecane (HBCD) and 11 congeners of PBDE. This study used breast milk as a proxy for maternal blood concentrations of chemicals. In an attempt to avoid the TSH surge that subsides within the first three days after birth, whole blood samples were taken from infants at 3 days after birth for all babies except two, one which was taken as 45 hours of age and the other taken at delivery. This study did not reveal an association between neonatal TSH concentrations and HBCD and PBDE contamination in human milk. One potential confounder was that the milk samples were obtained approximately one month after the TSH measurements. However, persistent organic pollutants in breast milk are known to decrease by only 2-3% per month according to previous research; after analysis was adjusted to reflect this, no statistical difference was found. This study was also limited by a lack of T_4 measurements.[25]

Organochlorines

A recent cohort study of the correlation of TSH status in neonates and prenatal exposure to organochlorine pesticides (OCPs) was inconclusive. The relationship examined was between levels of OCPs detected in placenta and TSH level measured in cord blood of newborns in Spain. The subjects included were originally selected to investigate the effects of maternal chronic pesticide exposure on urogenital deformations in newborn male babies. Of 700 pairs of babies and mothers, 308 placentas were randomly sampled for extraction and measurement of OCPs. TSH was measured in 551 of the boys. Covariate questionnaires identified many potential confounders. Complete information (OCP concentrations, TSH, and completed covariate questionnaire) was

obtained for 220 pairs of participants. Statistical models were adjusted to account for confounders identified in the questionnaire. A confounding factor not taken into account in this study was maternal nutritional status: the mothers' levels of iodine, selenium, and iron would have been of particular interest since these nutrients have been shown to have significant effect on thyroid hormone levels in other studies. A strong correlation between cord blood TSH levels at or above 5 mU/L and high placental levels of the OCP pendrin was discovered (odds ratio 2.05). However, high exposure to endosulfan sulfate was associated with much lower odds (OR 0.36) of elevated TSH. Another marginal negative correlation between hexochlorobenzene and TSH was found, while the other 15 OCPs examined showed no correlation with TSH levels.[57]

A recent longitudinal study examined the relationship between organochlorine compound (OC) exposure during fetal development and thyroid function; and between thyroid function and early childhood neurodevelopment. The study followed a birth cohort of 182 children in the Faroe Islands from birth to 5.5 years of age. Concentrations of OCs were assessed in the serum of mothers during pregnancy as well as in postnatal breast milk. Free T_3 (FT_3), FT_4, total T_4, free thyroxine index (FTi), resin T_3 uptake ratio (T_3RU) and TSH were measured in maternal and cord serum. T_3RU is an indirect measure of thyroxine-binding globulin (TBG) unsaturated by thyroxine; T_3RU is low in hypothyroidism and high in hyperthyroidism. OC exposures were inversely associated with T_3RU in pregnancy and at birth. No significant association was seen for other thyroid hormone levels. Iodine status of all participants was assumed to be sufficient, given that residents of the islands consume seafood regularly. It would have been useful to additionally test subjects for iodine and other key nutrients to rule out variations in these nutrients as confounders.[29]

Polychlorinated biphenyls (PCB)

A 2007 longitudinal birth cohort study in an agricultural area of California analyzed PCB concentrations in the blood of 285 pregnant women, as well as TSH levels of their newborns in the first few days after birth. This study showed found that not all

PBC congeners are thyroid hormone disruptors, but a subset of PCBs showed positive correlation with TSH levels in newborns and prenatal PCB exposure. Participant interviews provided socioeconomic and demographic information to identify potential confounders, including country of birth, time living in the United States, use of alcohol, drugs, tobacco or caffeine, and employment in agricultural work (which would result in high exposure to OCPs and other OCs). Statistical analysis tested associations of individual PCB congeners and of groupings of PCBs with blood TSH levels in the neonates. OCs were measured concurrently with PCBs. The results of this study bear further investigation and seem to correlate well with the disparate results of individual PCBs observed in the Freire, et al., study.[58, 57]

Perfluorocarbons

A study of NHANES data identified a positive association between thyroid disease and high concentrations of serum perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) in adults. Data from 3,974 participants in NHANES 1999-2000, 2003-2004, and 2005-2006 with perfluorinated chemicals detected in serum were analyzed, with adjustments made for age, gender, education, race, BMI, alcohol intake, and smoking. Laboratory collection and analysis methods were standardized across each NHANES year. Subjects were asked about any existing thyroid problems; anyone on thyroid medications was also classified as having thyroid disease. Mean PFOA and PFOS levels were found to be higher in men, and in people with a higher level of education. PFOA was also higher in people with higher alcohol consumption. A strong association with PFOA and women being treated for thyroid disease was identified. The odds ratio for self-reported thyroid disease in women was significantly higher for those the upper quartile of serum PFOA. In men a less significant association was found. There was an insignificant relationship between PFOS levels and thyroid disease in men but no association in women.[33]

The C8 Health Project found PFOA and PFOS to be strongly related to thyroid dysfunction. The C8 Health Project is a cross-sectional study that is evaluating thyroid

function (as measured by TSH, T_3 uptake, and thyroxine concentrations) of 52,296 adults with known exposure for at least one year to PFOA in drinking water from one of six water districts whose water was contaminated by effluent from the DuPont Works plant near Parksburg, West Virginia. Participants with diagnosed thyroid disease were excluded from analysis. Significant increases in serum thyroxine and significant decreases in T_3 uptake in association with PFOA and PFOS exposure were observed in all age groups (<20 to <50 years and >50 years of age) and in both genders. Serum PFOA and PFOS concentration were lowest in women 20-50 years of age, and were lower in women than in men overall. This study is ongoing, and a model for individual exposure in relation to thyroid diseases is still in the design process. Therefore, data on thyroid disease in relation to PFOA and PFOS will be reported in a future paper by these researchers. These results, however, highlight the need for studies on persistent organic compounds to analyze data separately for each gender. The authors speculate that one reason for higher PFOA and PFOS levels in men and postmenopausal women is that the younger women clear out some of the toxins with menses.[59]

Perchlorate

A large California study found that perchlorate exposure could result in a 23%-57% increase in the incidence of high TSH levels in newborns as compared with neonates in unexposed populations. All newborns in California have their TSH levels measured, usually within 48 hours after birth, as part of compulsory testing of neonates. Perchlorate is suspected to lower T4 production, leading to increased TSH secretion. This study examined the association between TSH and perchlorate using data from 497,458 California newborns. Screening for primary congenital hypothyroidism (PCH), which is caused by an underdeveloped or missing thyroid gland, uses a very high cutoff level of TSH of 25 μU/mL. This study sought to uncover less severe changes in TSH that may be a result of reduced T4 production and which still adversely effect neurodevelopment. California communities were classified as exposed (>5 mcg/L) or unexposed based on a data from 800 measurements of perchlorate in drinking water. The odds ratio for TSH levels at or above 8 μU/mL within 24 hours of birth in perchlorate-exposed areas as

compared with non-exposed communities was 1.27 ($P < 0.0001$). This suggests that perchlorate exposure may be a factor in increased TSH in newborns. For TSH levels of 25 and 15 μU/mL, ORs were 1.53 ($P < 0.0001$) and 1.23 ($P < 0.001$) respectively. Perchlorate exposure levels did not account for exposure to perchlorate in food nor use of alternate sources of water. However, the authors surmise that similarity in thyroid hormone data collection minimizes any misclassification confounding and that correction of the bias would yield higher ORs. Adjustments were made for other confounders (age at collection of TSH; gender, birth weight, ethnicity). However, iodine status was not available for study participants.[60]

A study using NHANES 2001-2002 data from 2,299 adolescent and adult participants examined the effects of perchlorate exposure on thyroid function. In women, significant relationships were identified between perchlorate and thyroid hormones dependent on iodine status. In women with urinary iodine < 100 mcg/L, perchlorate exposure was significantly associated with lower levels of total T_4 ($P < 0.0001$) and elevated TSH ($p = 0.001$). In women with urinary iodine > 100 mcg/L, perchlorate was significantly related to elevated TSH ($p = 0.025$), but did not correlate to changes in total T_4 levels ($p = 0.550$). This difference may indicate that iodine-deficient women are more vulnerable to perchlorate competition with iodine for uptake in the thyroid gland. In men, perchlorate exposure was not significantly associated with TSH or total T_4 levels regardless of iodine status. Statistical analysis was adjusted for confounding factors known to be associated with TSH and T_4 levels: age; hours of fasting; BMI; ethnicity; menopause; estrogen replacement therapy; pregnancy; menarche status; selected medications (thyroid hormones, anti-thyroid medications, beta blockers, steroids, furosemide); serum albumin, C-reactive protein, and cotinine (a marker of tobacco smoke exposure); and urinary nitrate and thiocyanate.[61]

A very underpowered study of 13 healthy, euthyroid volunteers found that daily doses of perchlorate up to 3 mg daily over six months did not affect thyroid function. No significant changes were observed in thyroid hormone, TSH, or Tg levels, or in the ability of the thyroid to take up iodine.[62]

Cigarette smoke

This Norwegian cross-sectional study analyzed a database of 20,479 women and 10,355 men to examine the relationship between smoking and thyroid dysfunction. Volunteers from an iodine-sufficient county completed a questionnaire asking about any diagnosed thyroid disease and about smoking habits (past smoking, type of tobacco smoked and amount, age when they began to smoke, and total years of smoking). Serum levels of TSH in all participants older than 40 years and a 5% random sample of 20-40-year-olds were measured. Free T_4 was measured in those whose TSH was > 4.0 mIU/L. Exclusion criteria among this subset of participants were reported thyroid disease and those missing information on smoking status. Overall, smokers had lower TSH levels with an increased incidence of hypothyroidism but an even more significant risk of hyperthyroidism. A dose-response relationship between "moderate" tobacco smoking (up to 12 cigarettes daily) and TSH level; heavier smoking was not found to further depress TSH. TSH levels in former smokers rose with time; in 10 years (for women) to 18 years (for men) after quitting, TSH levels were similar to those of subjects who had never smoked.[63]

In Greece, a small randomized, single-blind crossover study of 14 male and 14 female non-smokers tested the acute effects of secondhand cigarette smoke on sex hormones and thyroid hormones. After one hour in a normal-air environment, volunteers were exposed to one hour of moderate levels of secondhand smoke intended to simulate levels commonly encountered in bars and restaurants. In addition to significant decreases in progesterone and testosterone in men and marked decreases in progesterone and 17-beta estradiol in women, significant increases in serum free thyroxine was measured in both sexes. In men, free T_3 and T_4 increased significantly, while free T3-to-T4 ratio decreased significantly. In women, only free T4 significantly increased.[64]

More evidence for the negative effects of cigarette smoke on the thyroid gland was found in a study of a cohort of 237 women, divided into groups of smokers, nonsmokers, and secondhand smokers. Exposure from smoking and from secondhand smoke was found to cause mild inhibition of thyroid gland function. Self-reported smoke exposure was verified by measuring cotinine (a biomarker of recent tobacco smoke

exposure) in serum. Serum TSH, total T_3 and total T_4 levels were also measured; to control for monthly hormonal fluctuations of hormones, blood samples were drawn only during the follicular phase of each woman's menstrual cycle. Both active and passive smokers had significantly lower levels of TSH as compared with nonsmokers. T_3 and T_4 concentrations were also lower in both groups of smokers, but not significantly so.[35]

A large Swedish cohort study found that iodine deficiency was a significant predictor of risk of thyroid disease in smokers. 847,507 mothers were followed from 1983 to 1997 to examine associations between their tobacco-smoking history and the incidence of thyroid nodules and toxic or nontoxic goiter. No thyroid hormone measurements were taken as part of the study; diagnoses of thyroid disease were verified by the Swedish national Inpatient Registry database. Iodine status was estimated based on the geographical area where each woman was born. Some areas of Sweden suffered from endemic goiter until about 1950; about 16% of the women were born in these areas. This study would have benefitted from iodine and thyroid measurements for each participant, but given the large sample size, the estimate based on iodine status in populations over time may suffice here.[65]

Nitrates

A population-based cohort study in Iowa found an association between higher levels of nitrate in drinking water and an increase in thyroid cancer risk. This study evaluated 21,977 older women who, as of 1986, had all used drinking water from the same source for ten years or more. Nitrate intake from water was estimated from a public nitrate measurement database. The authors determined a significant association between a water supply containing over 5 mg/L of nitrate and increased thyroid cancer risk. With consumption of such water for five or more years, the relative risk of thyroid cancer rose to 2.6 (95% CI). A food frequency questionnaire was used to estimate nitrate intake. Participants with higher nitrate intake from foods were also found to have a greater incidence of thyroid cancer and hypothyroidism with increasing intake, but no relationship was found with hyperthyroidism. Other pollutants contaminating the water

could confound these results. For example, pesticides are ubiquitous in the agricultural region of Iowa from where the study's volunteers reside. Perchlorate is known to disrupt thyroid function as well. The authors did consider the latter and found that in private wells in Iowa, only one was found to be contaminated with perchlorate, but assume from this that the public water supply is also relatively free of this pollutant. In addition, participants were not screened for iodine status. The authors assumed iodine sufficiency based upon US population data from NHANES 1971-1974. Urinary nitrate levels were not evaluated.[36]

A cross-sectional epidemiologic survey found that dietary nitrate in the population of West Pomerania, Germany, was low overall, and was not associated with goiter. 3,772 adults without thyroid dysfunction were examined via thyroid ultrasound and measurement of urinary nitrate concentration. Interviews were conducted to categorize subjects by educational status; smoking behavior and BMI. Individual iodine status was not determined. Volunteers were divided into a low-nitrate group and a high-nitrate group. The mean urine nitrate concentration across both groups was 53.1 mg/L. The study authors defined high nitrate levels as the 75th percentile for the population investigated, or 69.0 mg/L. This region of Germany had been iodine-deficient and has only become iodine-sufficient in decade preceding the study. With a group of subjects aged 20-79 years, all participants had spent at least ten years of their childhood in an iodine-deficient state. Evidence of subsequent thyroidal effects was demonstrated by the relatively high goiter incidence found in these participants, similar in both subgroups: 35.5% in the low-nitrate group and 34.7% in the high-nitrate group. Based on previous studies, the water and food of West Pomerania supplies less than 125 mg of nitrate per capita daily, or about 1.6 mg/kg of body weight, which is significantly less than the amount of 3.65 mg/kg recommended by the World Health Organization. Smoking increased urinary nitrate concentrations and was higher in current smokers than in former smokers. Smoking did not affect thyroid volume or incidence of goiter in this cohort.[66]

A study of Bulgarian schoolchildren compared 156 children from a village with high levels of nitrate in the drinking water (75 mg/L) with 163 children from a village with low nitrate water levels (8 mg/L). Both villages had low levels of iodine in the soil

and water, and both had negligible levels of perchlorate in the water supply. Participants were evaluated for urinary iodine status and goiter. The median urinary iodine concentration for all children was sufficient (in girls) or excessive (in boys). Goiter prevalence in the low-nitrate group was 4.9%, while 13.5% of the high-nitrate group had goiter. The relative risk for thyroid dysfunction in nitrate-exposed children compared with those minimally exposed was significantly higher, with an odds ratio of 3.014 (95% CI).[67]

One very underpowered study tested for effects of acute, rather than chronic, nitrate exposure. Ten participants received 15 mg/kg of sodium nitrate daily for 28 days, while a control group of ten subjects were given distilled water. At baseline and at the end of the exposure, 5- and 24-hour thyroidal I-131 uptake tests were performed, as well as plasma measurement of T_3, reverse T_3, T_4, and TSH concentrations. The study found no significant difference between the nitrate-exposed group and controls after 28 days in any of these measurements. Most nitrate exposure in populations is at low doses over many years, and may have an additive effect over time. Therefore, a longer study would be more appropriate to real environmental exposures. Radioactive iodine uptake is not a valid test for chronic effects of nitrate or any other pollutant on thyroid function since the radiation exposure presents a significant confounding variable affecting thyroid health. Neither this study, nor any of the others reviewed here, account for the reduction of nitrate to nitrite and potentially to carcinogenic N-nitroso compounds. Future studies should be analyses of populations exposed over time to properly identify long-term effects for these variables.[68]

DISCUSSION

Various nutrients in addition to iodine are essential to thyroid function. Iodine supplementation in undernourished populations appears to have only partial success in reversing thyroid dysfunction depending upon the nutritional status of other micronutrients, in particular iron and vitamin A. Selenium has been studied more in better-nourished populations and appears to have a beneficial effect on thyroid function

in women with mild selenium deficiency, in particular those with autoimmune thyroiditis. To date, selenium supplementation appears to be of minimal benefit to men and children, but more gender- and age-specific studies are needed to build upon the meager few that have included these subjects. Additionally, the efficacy of sodium selenite should be compared to that of selenomethionine.

Iron appears to be essential for thyroid homoeostasis, independently of iodine and selenium status. Indeed, as these studies show, iodine supplementation in iodine- and iron-deficient populations is far less effective when not combined with iron treatment. In the few studies available on vitamin A and thyroid health in humans, vitamin A supplementation has been shown to increase the efficacy of iodine supplementation, reduce goiter and normalize all thyroid hormone levels in a significant number of children deficient in both nutrients. More study will be needed to verify this effect, which shows promise for public health programs in the most disadvantaged countries. Human studies on zinc and the thyroid are likewise rare, and they show mixed results. Iodine-replete children did not see any significant drop in goiter incidence from zinc supplementation, while adults of unknown iodine, iron, and selenium status appear to gain significant improvement in thyroid hormone levels in another study. More and better-designed trials are necessary to discover the real benefit of zinc to thyroid function.

Soy isoflavone trials have divergent outcomes as well, so the evidence is not clear regarding the safety of phytoestrogens for the thyroid gland. These tests suffer from a wide variety of isolated and concentrated compounds being tested. Future studies should focus on the whole food in amounts eaten in a normal diet, with amounts varying to reflect regional dietary differences. Testing a single isolated isoflavone in large amounts is not useful for determining potential harm from dietary intake.

Effects of phthalate and BPA exposure varied between adults and adolescents in the studies reviewed. In adults, total T_4 and thyroglobulin decreased and TSH increased with increasing phthalate and BPA exposure. Adolescents showed no changes in T_4 but had increases in T_3 in addition to TSH. Some specific bioesters, such as monobutyl phthalate (MBP) in one reviewed study, are found to have more potent effects on thyroid

hormones than others examined. More research is needed on specific bioesters or congeners of phthalates and BPA in age- and gender-specific studies.

Some congeners of PBDE are associated with subclinical hyperthyroidism in pregnant women. Other studies have not found significant correlations between PBDEs in general and thyroid hormone concentrations in adults or in newborns.

Overall assessment of OC effects on the thyroid appears to be inconclusive. However, when effects of individual OCs are isolated, more definitive associations appear, such as a finding of double the odds of elevated TSH in cord blood associated with high placental levels of the OC pesticide pendrin in one study. The single study that assessed resin T_3 uptake ratio (T_3RU) was able to detect an inverse association between general OC exposure and T_3RU in pregnant women and their newborns, potentially indicating subclinical hypothyroidism.

A relationship between PCBs and thyroid hormones has been suggested in both animal and human studies. However, results vary depending on whether PCB and thyroid hormone levels were measured in maternal blood, placenta, infant blood, or cord blood. Another confounder among these studies is that they examined different PCB congeners or grouped them using different methods.

The perfluorocarbons PFOA and PFOS have shown strong positive associations with thyroid disease in large-scale studies on adults. While higher levels of these chemicals have been found in men, women exposed to PFOA and PFOS appear to have a higher incidence of thyroid disease. Differences in PFOA and PFOS concentrations were seen between pre- and post-menopausal women as well.

Perchlorate exposure has been strongly associated with elevated TSH levels in newborns and women, with T_4 also decreasing in those who are iodine-deficient.

Cigarette smoking has been shown to depress TSH and increase risk of hyperthyroidism. Acute exposure to second-hand smoke for just one hour was found to significantly increase T3 and T4, while chronic exposure decreased levels of these hormones. Studies have not sought to identify the specific compounds responsible for

these effects. This may be a formidable task due to the great number of chemicals present in cigarettes.

High levels of chronic nitrate exposure appear to increase thyroid cancer risk and increase goiter incidence in iodine-deficient people. Low-level and acute exposure may not have observable effects. More and larger studies are needed on thyroidal effects of nitrates in highly exposed populations would verify these findings.

CONCLUSION

The large number of congeners extant for each chemical complicates the study of most of the compounds reviewed here. For compounds such as PBDE, OCs, PCBs, perfluorocarbons, and perchlorate, future studies should focus on isolating the effects of individual congeners and identifying synergistic thyroid-disrupting effects of chemicals commonly found together. Gender differences have also been observed for many of these compounds, underscoring the need for separate data analyses for males and females. Age is also a factor, with the thyroid function of children being more sensitive to contaminants than adults, and that of post-menopausal women more susceptible than pre-menopausal women to many these chemicals. Future studies that consider all these factors will be of the most use to public health administrators and clinical practitioners.

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