Endocrine disruptors and thyroid autoimmunity

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ABSTRACT

Many papers evaluated the effect of the environmental, or occupational endocrine disruptors (ED), on the thyroid gland, that can lead to thyroid autoimmunity. A higher prevalence of "autoimmune thyroid diseases" (AITD) was observed in people living in polluted areas near to petrochemical plants, and in petrochemical workers, but also in area contaminated with organochlorine pesticides, or with polychlorinated biphenyls, or near aluminum foundries. The exposure to Hg in chloralkali workers, or in swordfish consumers has been also found to increase AITD prevalence. Vanadium has been shown to increase the inflammatory response of thyrocytes. A beneficial effect of omega-3 fatty acids, and of myo-inositol and selenomethionine have been shown to counteract the appearance of AITD in subjects exposed to environmental or occupational ED.

More large studies are needed to investigate the potential roles of ED in the induction of AITD, and of agents or habits that are able to prevent them.

Keywords: Autoimmune thyroid diseases; autoimmune thyroiditis, Graves' disease; endocrine disruptors; myo-inositol; selenium/selenomethionine

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Historical note: the term "endocrine-disruptor"

The term "endocrine disruptor" was conied during the meeting organized by the late Dr. Theo Colborn at the Wingspread Conference Center Racine, Wisconsin, USA, in July 2011. Participants included experts in the fields of anthropology, ecology, comparative endocrinology, histopathology, immunology, mammalogy, medicine, law, psychiatry, psychoneuroendocrinology, reproductive physiology, toxicology, wildlife management, tumor biology, and zoology.

In regard to the said term, some sentences appear in the "Statement from the Work Session on Chemically-Induced Alterations in Sexual Development: the Wildlife/Human Connection" (1). One important sentence is "*Many compounds introduced into the environment by human activity are capable of disrupting endocrine system of animals, including fish, wildlife, and humans. The consequences of such disruption can be profound because of the crucial role hormones play in controlling development*." (1). Incidentally, to celebrate the 20th anniversary of this important conference, one of us (S.B.) organized the International Workshop on "The Endocrine Disruptors: What the Scientists, Physicians, Politicians and People Need to Known on What's Going on in the Environment" (September 7-9, 2011, Montalbano Elicona, Sicily, Italy). The reference to this workshop is pertinent because S.B. presented the initial data on a study related to thyroid autoimmunity which is summarized later on in this article (2).

Four years later, at a workshop organized in Raleigh, North Carolina (April 10-13, 1995) by the U.S. Environmental Protection Agency (EPA), the definition given for an endocrine-disrupting compound was as "*an exogenous agent that interferes with synthesis, secretion, transport, metabolism, binding action, or elimination of natural blood-borne hormones that are present in the body and are responsible for homeostasis, reproduction, and developmental process* (3)". According to the 2009 Scientific Statement of The Endocrine Society, "*an endocrine-disrupting substance is a compound, either natural or synthetic, which, through environmental or*

inappropriate developmental exposures, alters the hormonal and homeostatic systems that enable the organism to communicate with and respond to its environment" (4).

Thyroid autoimmune disorders: children of a lesser God in previous reviews

Autoimmune thyroid diseases (AITD) are organ-specific autoimmune disorders mediated by T helper (Th)1 lymphocytes, whose main clinical presentations are Hashimoto's thyroiditis (HT), or Graves' disease (GD), characterized respectively by hypothyroidism, or thyrotoxicosis.

Several environmental risk factors (such as, radiation, smoking, viruses, iodine, stress, drugs, seasonality) are took in account as triggers of AITD in susceptible individuals (5-7).

As evident from the above definition for an endocrine-disrupting substance (4), endocrine autoimmunity is missing. The subsequent lines of the present article show that AITD are missing or are given limited space (as if they were children of a lesser God!) in other reviews available in the literature.

The first comprehensive review on the negative consequences for the thyroid that are exerted by synthetic chemicals dates back to 1998 and was written by the endocrinologist Francoise Brucker-Davis when temporarily working at the World Wildlife Fund, Washington, D.C., USA (8). Excluding Bibliography, in the 20 pages of text (pages 827-846, two-column layout, each column consisting of 62 lines) only one 32-line paragraph of it was devoted to Thyroid Autoimmunity in the three page-long section entitled Mechanisms of action. This paragraph contained only 9 citations of the literature, or 2.4% of a total of 381 references listed in the review (8). In her most recent review on the topic, but in French language, starting from the Abstract she acknowledges that "in adults the main concerns [of endocrine disruptors (ED)] are tumor/goitrogenesis and autoimmune thyroid disease" (9). In Table II **[entitled "Points d'impact possible des perturbateurs thyroïdiens"**], under the level of action of "autoimmune process" these substances are reported: "polybrominated diphenyl ethers (PBDE), méthylcholantrène, furanes, polychlorinated biphenyls (PCB)" **(9).** Only one reference is cited which is, in turn, a review (**9,**10). In Table 1

[entitled “Table 1. Partial List of Environmental Agents That Interfere with Thyroid Function”], of 8 entries (PCB, organochlorine pesticides, PBDE, Bisphenol-A (BPA), perchlorate, thiocyanate, triclosan and isoflavones), for 5 of them (organochlorine pesticides, BPA, perchlorate, thiocyanate and triclosan) the comment “No human studies establishing association” appears in the column “Associated as a trigger or accelerating autoimmune thyroid disease”. For PBDE, the comment is “*Increase in HT in some studies*”; for isoflavones, the comment is “*Possible increase in HT*”, while for PCB, the comment is “*Possible increase in TSH, thyroid autoantibodies, thyroid volume*” (10). In this review, the fundamental section (which is entitled “Environmental toxicants”) occupies less than one page and contains only 8 references. That review also deals with cigarette smoking, which is disregarded in our present review, by reminding the readers that cigarette smoking increases the risk of GD and Graves’ ophthalmopathy (GO), but reduces the risk of HT (10).

In the year 2009 an interesting review was published, but is was mostly focused on “*a unique animal model, the NOD.H2h4 mouse to explore the influence of iodine and other environmental factors on autoimmune thyroiditis*” (11). Upon citing old literature (12-15), Burek and Talor highlight that autoimmune thyroiditis-prone rodents develop thyroiditis with increased frequency when exposed to polyaromatic hydrocarbons such as methylcholanthrene or 7,12-methylbenz(a)anthracene (11). Finally, using KBr as a surrogate for polybrominated biphenyls (PBB), Burek and Talor show that bromine may exacerbate autoimmune thyroiditis in the NOD.H2h4 mouse (11).

In the year 2009, an encyclopedic review by Diamanti-Kandarakis, an *ad hoc* Task force of The Endocrine Society was published (4). The review consists of 34 pages of text distributed in two columns of 52 lines each. Only in the one-page long subheading “Environmental chemicals impacting thyroid function”, there is a sentence alluding to thyroid autoimmunity, *“In addition, teenage children diagnosed with autoimmune thyroid disease were found to have twice the rate of occurrence if they had consumed soy formula as infants* (16).” That reference is an American paper based on detailed history of feeding practices in 59 children with AITD, their 76 healthy siblings,

and 54 healthy nonrelated control children (16). No other reference is made to thyroid autoimmunity in the remaining three pages dedicated to the influence of the ED on the thyroid (4). Even at the 2018 annual meeting of The Endocrine Society (Chicago, IL, 17-20 March 2018), the issue of ED and thyroid autoimmunity was neglected. Yet, there was a 4-presentation symposium entitled “Endocrine Disruption in Health and Disease: What do we Know and What's Missing”, another 4-presentation symposium entitled “Novel Facets of Autoimmune Thyroid Disease”, a 6–presentation Oral Session entitled “What's New in Endocrine Disruption”, a 7-presentation Oral Session entitled “Benign Thyroid Disease”, and about 30 posters in the section “Endocrine Disruption” and about 40 posters in the section “Clinical Facets of Thyroid Disease”.

As of 30 June 2019, a PubMed search on “endocrine disruptors AND thyroid” returned 803 items. The latest reviews (17-22) continue to disregard thyroid autoimmunity.

It was therefore with great excitement that S.B. and A.A. accepted the invitation by the issue Editor Evanthia Diamanti-Kandarakis to prepare a review for the December 2015 issue, entitled “Endocrine Disrupting Chemicals – is it time to act?” (23). We take again the opportunity to acknowledge the quick acceptance of the proposed review by Prof Diamanti-Kandarakis based on the arguments that this topic was neglected in the aforementioned review (4) and continued to be neglected in subsequent reviews published until that time (see above).

Something happened to Hashimoto’s thyroiditis in the mid-90’s

Two striking phenomena, that concerned the most frequent autoimmune disorder and that passed unnoticed in the scientific thyroid community, ignited the interest of S.B. on the topic of endocrine disruptors and thyroid autoimmunity. These phenomena were major stimulators of the research associated with reporting a modified presentation of patients with HT over 3 decades at the Division of Endocrinology, university hospital of Messina, Sicily (24). One phenomenon was that the female to male ratio in series of patients with HT published in the literature between the years 1980 and 2015 continued to decrease. Indeed, the Pearson’s coefficient of correlation was = -0.566, (P=

0.009), but it had been -0.486 (P< 0.05) for the years 1980-2006. The second phenomenon was the earlier age at presentation in the Endocrine Division of the HT patients. Indeed, the Pearson's coefficient of correlation was -0.831 (P<0.0001) but it had been -0.738 (P<0.001) for the years 1980-2006. Practically, upon comparing the period 2001-2005 with the period 1975-1979 (data given as mean SD), the number of HT patients observed at that Division of Endocrinology increased by 13 times (from 33±2.4/year to 444±41/year), age at presentation was one decade younger (from 50.9±2.1 years [median 50.5]; to 41.7±0.5 [median 41.2]), and the representativity of males increased by 3 times (F:M ratio from 20.6±9.4:1, to 7.8±0.7:1) (24). The trends of data were confirmed independently at the Cytological Unit of the same university hospital, upon evaluating the cytological diagnosis of HT [chronic lymphocytic thyroiditis (CLT)] in outpatients referred for the evaluation of thyroid nodules by ultrasound-guided fine-needle aspiration (FNA) (25). Here data started to be computerized in 1988, so that the reference period was 1988-92. At this time, frequency of the cytological diagnosis of CLT was 1.2%, which jumped to 7.1% in 2003-2007. Age of patients at FNA and F:M ratio decreased from 51.4 ± 14.9 years and 24.0:1, to 46.6 ± 15.0 years and 8.3:1. Noteworthy, the frequency of the cytological diagnosis of a non-autoimmune thyroiditis (namely, De Quervain or subacute thyroiditis) remained stable (25).

Therefore, we aimed to deepen these changes evaluating also the possible correlation with the ED. In a retrospective study, we recorded the incidence of HT and thyroid cancer (TC) in two close areas of the Sicily. We observed differences in the two areas, both in the time of the onset of the pathologies and also in their incidence, probably due to the different intensity to the exposure to same environmental factors (26). This study underlined the importance to better investigate the environmental factors able to trigger these pathologies and to influence their course.

Finally, for sake of completeness, another change in HT that had hit S.B. was the increasing frequency in the association of HT with chronic idiopathic urticaria (27), urticaria also having a relationship with endocrine disruptors, particularly in the occupational setting (28).

Were similar phenomena reported in the literature for non-thyroid autoimmune diseases?

Similar phenomena about incidence, gender and age distribution were reported also for other autoimmune diseases. For example the predominance of Multiple Sclerosis (MS) in females is increasing, it changed over the time from an equal prevalence (29) to a rate of 2:1 (female:male) (30) and recently it raised up to 3:1 (31), and it has been shown that environmental factors gave their contribution to this change (32,33).

Some differences were reported for other disorders, such as the neurological ones, in fact recent data obtained from different country like Japan, China and India, suggest a greater prevalence of Guillain–Barré syndrome in males (32); another disorder observed more frequently in males is the ankylosing spondylitis (32).

Females continues to maintain their primacy for endocrine related diseases, including GD and HT, whereas for type 1 diabetes the prevalence reaches the parity, although it geographically varies favoring males in the USA and Denmark, or females in Japan and Australia (32).

Generally, celiac disease is more frequent in female, although dissimilar outcomes were observed in India with a higher prevalence in males (32).

Similar prevalence between genders were observed for ulcerative colitis and Crohn's disease, however Asakura et al. showed a trend towards male in Japan (70% Crohn's disease) (32).

The observed disparity could be due to a difference in the type of exposure to environmental chemicals and also in the type of biological response to these agents, that lead to different autoimmune diseases (32).

Thyroid autoimmunity and endocrine disruptors

The different increase of autoimmune disorders (including type 1 diabetes mellitus, MS, AITD, and inflammatory bowel diseases), between Western industrialized countries and those defined as

"developing", shed a light on the dangerous effects of environmental and/or occupational factors (23).

There are indeed data in the literature on the effects caused by polluting chemicals on indices of thyroid autoimmunity, either in an occupational or environmental setting (Table 1).

Environmental settings

In Beijing, defined as the city with the most polluted air, was recorded an increase rate of differentiated thyroid cancer (DTC) of about 538.7 % (23).

Food or drink contamination contributes to the development of AITD, as observed in a study about Caucasian pregnant women, thyroid disease-free, nonsmoker, having different dietary habits. Lower thyroid autoantibodies were associated with those consuming oily fish containing a major quantity of omega-3 fatty acids, on the contrary of those eating swordfish that contains substances like Mercury (Hg), which counteract the protective effect of the good ones (2).

An increased frequency of subclinical thyroid disorders and a rise of thyroid volume, were found in children who drunk contaminated water with nitrate and ate meals whose products derived from high nitrate area (34).

Endocrine disruptors could cause an increase of thyroid hormones antibodies (THAb) levels also in patients with other non-thyroidal autoimmune disorders, such as Vitiligo. Therefore, an evaluation of thyroid function is highly suggested, also in these types of patients (35).

Further investigations examined the effects caused by polluting chemicals on indices of thyroid autoimmunity, in an environmental setting. It was carried out a study comparing two areas of the Sicily, one of which characterized by a more polluted atmosphere with high concentrations of heavy metals, due to petrochemical complex, and also with a higher frequency of CLT, with respect to a control area (36). The rate of suspicious or malignant cytology of thyroid nodules was double in the most contaminated area, with an upward trend toward malignant cytological classes (36).

Several studies obtained the same evidences by finding high incidence of thyroid Abs in subjects living in area surrounding petrochemical complex, or in rural area heavily contaminated with organochlorine (OC) pesticides, or near aluminum foundries (37-39).

Nevertheless, different results arose from another study according to which no differences were found about the autoimmune thyroiditis prevalence between area near petrochemical complex, *vs.* a control area (40).

Vanadium (V) is a grey metal that exists in a number of different states of oxidation, whose most common form in commercial products is vanadium pentoxide (V2O5). All vanadium compounds have been considered toxic. Recently the increase of TC incidence in volcanic areas suggested a carcinogenic effect of volcanic pollution. In the Mount Etna volcanic area TC incidence was higher, than in the control areas. In the volcanic areas various trace elements were increased (with respect to control areas) in both lichens and drinking water, indicating atmospheric and water pollution, among them V was increased 8 times, and its possible carcinogenic role on the thyroid was hypothesized. Recent studies showed that V2O5 is able to induce the secretion of Th1 chemokines into the thyroid, synergistically increasing the effect of Th1 important cytokines such as interferon (IFN)-γ and tumor necrosis factor (TNF)-α, leading to the induction and perpetuation of an inflammatory reaction into the thyroid (41-45).

A study investigated whether maternal heavy metal exposure affects their thyroid hormones and if have effects on fetal growth. Six hundred and seventy-five women were enrolled and their thyroid hormones as well the concentrations of heavy metals in their urine were tested. They showed that maternal exposures to V, arsenic, and lead at early pregnancy were associated with decreased maternal FT3 or FT3/FT4 ratio, which might contribute to reduced birthweight (46).

Occupational settings

Several studies highlighted also a genetic predisposition to the development of autoimmune disorders. Some associations were shown between polymorphism of the gene type 2 diodinase (DIO2) (274A > G) and elevated levels of antibodies against thyroid peroxidase (TPO), and that of TPO gene (2173A > C) with elevated levels of free T4, in women working with the oil organic synthesis plant (47).

Another study showed that petrochemical industries workers were at higher risk of reproductive and thyroid diseases with respect to control groups, in particular if carrying polymorph variants of CYP1A1 and CYP1A2 genes (48).

A Slovakian study, reported an increase of thyroid volume as well as of thyroid disorders in workers exposed for a long time to PCBs and other OCs (polychlorinated dibenzodioxins and dibenzofurans), with respect to controls extracted from less polluted areas (49). The Authors aimed to evaluate the effect of these chemicals also as environmental pollutes, revealing a positive association of autoimmune thyroiditis with OC levels (50).

Similarly, workers subjected to PBB exposure, analogs of PCB, showed elevated thyroid autoantibodies and serum TSH levels (51).

A study, involving chloralkali workers who were exposed to Hg vapor (able to inhibit the DIO2) revealed a reduction, in these subjects, of the serum FT4/FT3 ratio (52).

During the Vietnam war, a herbicide [Agent Orange, a mixture of 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid, contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)] was used for military purpose. Vietnam veterans exposed to this Agent Orange were more frequently affected by diabetes mellitus, and various disorders of the thyroid gland and pituitary gland, showing also an approximately 3-fold higher prevalence of the diagnosis of GD, compared to controls (53,54).

Is thyroid autoimmunity triggered by endocrine disruptors preventable and/or counteractable?

We tried to answer to this question with a study aimed to evaluate if changes in dietary habits in pregnant women could lead to different outcomes related to postpartum thyroiditis and depression (that is also linked to circulating thyroid autoantibodies) (2,55). The study was carried out in the South of Italy enrolling women who were consumers of swordfish, or oily fish, or of other fish. The swordfish consumers reported the worst thyroid profile with high levels of thyroid autoantibodies, this was primarily related to Hg, that is the principal contaminant of swordfish. Conversely, the higher protection from thyroid autoimmunity occurred in oily fish eaters. These two groups differed mainly for the estimated intake of omega-3 fatty acids, that should account for most of the thyroid autoantibodies suppression, and also, but in insignificantly manner for the estimated intake of selenium. Therefore, since serum autoantibodies correlated with the fish consumption, changing dietary habits could aid in lowering the rate of postpartum thyroiditis and depression (2,55).

Myo-inositol (Myo) and selenium/selenomethionine (SelMet) showed also protective effects in euthyroid patients with autoimmune thyroiditis, leading to a decline of TSH (overall in patients with an initial TSH value in the high normal range), and of the antithyroid autoantibodies levels (55). Indeed, Myo and phosphatidylinositol(s) cover an important function in many metabolic pathways, that, when impaired, exert negative effects in humans. It was shown that both the molecules are involved in physiological and pathological conditions of the thyroid gland, like thyroid autoimmunity.

Also, selenium has an important role in thyroid autoimmunity, indeed regions with severe selenium deficiency, registered an increased prevalence of autoimmune thyroiditis (56).

In a subsequent study, we assessed that the association Myo+Sel-Met was able to protect blood mononuclear cells, obtained from HT patients, to H2O2-induced oxidative stress (57).

Beneficial effects of Myo (58,59) or selenium/SelMet (60-65) towards protection from heavy metals have been reported also in animals.

More recently Myo, was evaluated in mice kidneys after cadmium (Cd) challenge, showing a protection against Cd-induced damages in mice kidney and suggesting a strong antioxidant role of this nutraceutical against environmental Cd harmful effects (66).

Conclusions

The issue of ED and thyroid autoimmunity was initially neglected. Indeed, in the first definition of endocrine-disrupting substance, endocrine autoimmunity is missing.

Many papers evaluated the effect of the environmental or occupational ED on the thyroid gland that can lead to thyroid autoimmunity. A higher prevalence of AITD was observed in polluted areas near to petrochemical plants, and in petrochemical workers, but also in rural area heavily contaminated with OC pesticides, or near aluminum foundries (37-39). The herbicide Agent orange was associated with a higher prevalence of GD in exposed military personnel (53,54). The exposure to Hg in chloralkali workers (52), or in swordfish consumers has been also found to increase also AITD prevalence (2). Vanadium has been shown to increase the inflammatory response of thyrocytes (41,42). Polychlorinated biphenyls and other OCs (polychlorinated dibenzodioxins and dibenzofurans), were associated with AITD in occupational settings, such as in polluted areas (49).

A beneficial effect of omega-3 fatty acids in the diet, and of the administration of Myo and selenium/SelMet have been shown to exert a protective effect against ED, contrasting the appearance of AITD in subjects exposed to environmental or occupational ED pollution (2,55).

More large studies are needed to investigate the potential roles of ED in the induction of AITD, and of agents or habits that are able to prevent them.

Conflict of Interest

The Authors have nothing to declare.

Role of the funding source

The Authors have nothing to declare.

Summary

Despite the issue of ED and thyroid autoimmunity was initially neglected, later on several studies showed an increased in the AITD prevalence in subjects exposed to ED. The exposure to ED could occur through different ways, by: 1) environmental pollution, in people living near to petrochemical plants, or in rural area heavily contaminated with organochlorine pesticides, or near aluminum foundries (37-39); 2) occupational exposure, as observed in chloralkali workers, or in military personnel exposed to the herbicide Agent orange (52-54); 3) food and drink contamination, as shown in swordfish consumers (2).

A protective effect against ED has been shown by omega-3 fatty acids in the diet, and by the administration of Myo and selenium/SelMet, that can therefore counteract the appearance of AITD in subjects exposed to environmental or occupational ED pollution (2,55).

More large studies are needed to investigate the potential roles of ED in the induction of AITD, and of agents or habits that are able to prevent them.

Practice Points

-Increased of AITD prevalence in subjects exposed to ED for an environmental, or occupational motif.

-A protective effect against ED has been shown by omega-3 fatty acids in the diet, and by the administration of Myo and selenium/SelMet.

Research Agenda

-More large studies are needed to investigate the potential roles of ED in the induction of AITD, and of agents or habits that are able to prevent them.

-More large studies are needed to investigate the potential agents or habits that are able to prevent the induction of AITD by ED

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Table 1. Occupational or environmental endocrine disruptors exposure and "autoimmune thyroid disorders".

Authors	Country	Setting and study groups	Findings
Benvenga S et al. (2)	Italy	236 women divided in 4 groups on the basis of eating habits, in particular group A (swordfish eaters) and group B (oily fish eaters)	Rates of both TPOAb and TgAb the highest in group A and the lowest (absent) in group B. Estimated content of mercury in the fish consumed monthly was about 1,000 mcg for group A and 25 mcg for group B.
Tajtakova M et al. (34)	Slovakia	324 schoolchildren from a high nitrate area (HNA) compared *vs* control groups: 168 from a neighboring low nitrate area (LNA); and 596 from the city of Kosice located in the vicinity of LNA.	TPOAb positivity, thyroid hypoechogenicty and TSH greater in HNA schoolchildren than in controls.
Colucci R et al. (35)	Italy	70 patients with Vitiligo were asked about their exposure to thyroid disrupting chemicals.	Frequency of positivity for at least one THAb very high, mostly against both T3 and T4. PCB exposure was positively associated to T4IgG, while exposure to nitrate, thiocyanate and soy isoflavone was positively associated with IgMT3+IgGT3.
Arena S et al. (36)	Italy	Cytological evidence of CLT in 1323 thyroid nodules interrogated by US-FNA of 1013 outpatients. 391 patients (490 nodules) resided in the zone of the petrochemical complex (zone A). The remaining 622 patients (833 nodules) were the controls, 15 km from zone A (zone B)	Frequency of CLT significantly greater in either patients or nodules from zone A *vs* zone B. Frequency of CLT was significantly greater in the suspiciously malignant + malignant classes (zone A *vs* zone B), but not in the benign+intermediate classes (zone A *vs* zone B).
de Freitas CU et al. (37)	Brazil	Subjects from an area surrounding a petrochemical complex *vs* a control area with steel industries	Prevalence of thyroid Ab and HT greater than in the control area.
Freire C et al. (38)	Brazil	Adults from a rural area heavily contaminated with organochlorine pesticides.	Higher frequency of TPOAb positivity. In males, TPOAb positivity correlated directly with exposure to methoxychlor.
Schell LM et al. (39)	USA, Canada	115 adolescents of the Akwesasne Mohawk Nation, which is situated on the St. Lawrence River with territory in New York State. Aluminum foundries, have contaminated the St. Lawrence River and its three tributaries. As a result, PCBs, p,p'-DDE, HCB and mire have entered the local food chain.	High rate of TPOAb positivity. 47 participants had been breast fed, among these, those with elevated TPOAb levels had significantly higher levels of all PCB groupings, with the exception of levels of non-persistent PCBs. Participants who were breast fed showed significant, positive relationships between TPOAb levels and all PCB groupings, except groups comprised of non-persistent PCBs, and with p,p'-DDE, HCB, and mirex.
Camargo RY et al. (40)	Brazil	409 subjects from an area neighboring a large petrochemical complex *vs* 420 control subjects from.	Prevalence of AIT in the petrochemical compex area statistically similar to that of the control area (15.6% *vs* 19.5 %).
Fallahi P et al. (41)	Italy	*In vitro* study evaluating the effect of vanadium pentoxide (V2O5) on thyroid cell viability and proliferation, and chemokine CXCL8 and CXCL11 secretion in normal thyrocytes.	V2O5 had no effect on thyroid follicular cell viability and proliferation, while was able to induce the secretion of CXCL8 and CXCL11 chemokines from thyrocytes. This may lead to the induction and perpetuation of an inflammatory reaction in the thyroid.
Fallahi P et al. (42)	Italy	*In vitro* study evaluating the effect of vanadium pentoxide (V2O5) on thyroid cell viability and proliferation, and chemokine CXCL9 and CXCL10 secretion in normal thyrocytes	V2O5 had no effect on thyroid follicular cell viability and proliferation, while was able to induce the secretion of CXCL9 and CXCL10 chemokines from thyrocytes. This may lead to the induction and perpetuation of an inflammatory reaction in the thyroid.
Sun X et al. (46)	China	Concentrations of heavy metals in urine samples and thyroid hormones in blood samples of 675 pregnant women were measured during early pregnancy in a cohort study.	Maternal exposures to V, As, and Pb at early pregnancy were associated with decreased maternal FT3 or FT3/FT4 ratio, which might contribute to reduced birthweight.
Kochetova OV et al. (47)	Russia	Female workers from an oil organic synthesis plant *vs* a control group	Association of polymorphic variants of the gene DIO2 (274A > G) with elevated levels of TPOAb.
Irmiakova AR et al. (48)	Russia	Women of a petrochemical industry *vs* control	Homozygous deletion of T base (−2467T/delT) of CYP1A2 gene is a liability marker for AIT.
Langer P et al. (49)	Slovakia	238 employees (age median 44) from a factory, which had produced PCB until 1985, *vs* 572 control adults from 3 much less polluted areas.	In female employees the frequency of TPOAb positivity was greater than in controls. The frequency of TgAb positivity in females employees (aged 31-60 years), was

		454 adolescents from the surrounding area polluted by PCBs *vs* 965 adolescents from 3 less polluted areas.	greater than in controls. In both male and female employees, TSHRAb was greater than in controls.
Langer P et al. (50)	Slovakia	2,046 adults who live in a polluted district *vs* adults from two neighboring upstream and upwind districts of background pollution	Thyroid hypoechogenicity, increased levels of TPOAb and TSH were positively associated with organochlorine levels, especially in males.
Bahn AK et al. (51)	USA	35 male workers exposed to PBB (analogs to PCB) and tetrachlorodibenzo-p-dioxin *vs* 89 controls.	Higher levels of TSH, MAb and TPOAb were found in workers.
Barregård L et al. (52)	Sweden	41 workers (aged from 18 to 61) exposed to mercury vapor for 1-20 years *vs* 41 age-matched unexposed controls.	No statistically significant association between occupational or environmental setting and mercury exposure indices.
Yi SW et al. (53)	South Korea	A total of 111,726 Korean Vietnam veterans were analyzed for prevalence of diseases of the endocrine system and other systems (data from January 2000 to September 2005). Agent Orange exposure was assessed by a geographic information system-based model.	Hypothyroidism, AIT, diabetes mellitus, other endocrine and non-endocrine disorders had adjusted ORs significantly higher in the high exposure group than in the low exposure group.
Spaulding SW (54)	USA	About 225,000 veterans of Vietnam era *vs* controls (veterans who served somewhere else).	The prevalence of Graves' disease was up to 3 times higher in the veterans exposed to defoliants with respect to the controls.

Abbreviations: Ab= autoantibodies; AIT= autoimmune thyroiditis; As= Arsenic; CLT= chronic lymphocytic thyroiditis; CXCL: chemokine (C-X-C motif) ligand; DIO2= deiodinase type 2; HCB= hexachlorobenzene; HT= Hashimotos' thyroiditis; MAb= microsomal autoantibodies; OR(s)= odds ratio; Pb= lead; PBB= polybrominated biphenyls; PCB= polychlorinated biphenyls; p,p'-DDE= p,p'-dichlorophenyldichloroethylene; TgAb= thyroglobulin autoantibodies; THAb= thyroid hormone autoantibodies; TPOAb= thyroperoxidase autoantibodies; TSHRAb= TSH receptor autoantibodies; US-FNA= ultrasound-guided fine needle aspiration; V= vanadium.