

IODIO - IODINE

- Gheidarloo M, Kelishadi R, Hovsepian S, Keikha M, Hashemipour M.

The association between prenatal exposure to organochlorine compounds and neonatal thyroid hormone levels: a systematic review. *J Pediatr Endocrinol Metab.* 2020 33: 21-33. doi: 10.1515/jpem-2019-0336.

In this systematic review, the association between prenatal exposure to organochlorine pesticides (OCPs) and neonatal thyroid hormone levels was studied. A systematic search of scientific literature was performed from the PubMed, SCOPUS and ISI web of science electronic bibliographic databases. The search strategy for the review was [(organochlorine OR "organochlorine pesticides" OR "organochlorine pollutants" OR "organochlorine pollutant") AND ("thyroid hormone" OR triiodothyronine OR Thyroxine OR "fetal thyroid function" OR "thyroid function" OR "Thyroid Stimulating Hormone" AND "prenatal" AND "maternal exposure")] in English sources. In this review, 305 papers (PubMed: 30; Scopus: 29; ISI: 246) were identified through an electronic database search. Twenty-seven articles were assessed for eligibility, from which 16 qualified articles were selected for the final evaluation. The most common OCP metabolites which were evaluated in order were hexachlorobenzene (HCB) (13 studies), pp-dichlorodiphenyldichloroethylene (pp-DDE) (13 studies), hexachlorocyclohexane (HCH) (10 studies) and dichlorodiphenyltrichlorethane (DDT) (eight studies). A review of the documents related to the association of prenatal exposure of OCPs with fetal or neonatal thyroid function tests provides us with heterogeneous data in this field. Factors such as differences in the studied populations and their area, ethnic and genetic background, time and rate of exposure, possible interaction of other thyroid-disrupting environmental factors and dietary intake of micronutrients such as iodine and/or selenium are considered the main limitations for making an accurate conclusion. For some OCPs including DDT, DDE, HCH and HCB, there are supporting evidences, and it is suggested that their exposure could potentially alter the fetal thyroid function and consequently impair the neurodevelopment process of the infants.

- Honglian Y, Huanliang L, Wei Z, Xiaojun S, Xiujie G, Kefeng M, Kun W, Bo C, Yanjun F, Zhuge X.

Thyroid-disrupting effects and mechanism of thiazole-Zn-induced thyroid cell hypertrophy and hyperplasia in male Sprague-Dawley rats. *Ecotoxicol Environ Saf.* 2020 196: 110544. doi: 10.1016/j.ecoenv.2020.110544.

Thiazole-Zn is a systemic fungicide synthesized and developed in China that has been used for the prevention and treatment of bacterial and fungal diseases on fruits and vegetables. Thiazole-Zn is a new thyroid disruptor chemical. The purpose of this study was to clarify the thyroid-disrupting property of thiazole-Zn and the mechanism responsible for thyroid hormone (TH) biosynthesis inhibition in male rats induced by thiazole-Zn. First, the effects of different thiazole-Zn doses and exposure times on the thyroid weights, thyroid morphology and serum hormone levels of rats were investigated. The results showed that thiazole-Zn increased thyroid weights and serum thyroid-stimulating hormone (TSH) levels and induced thyroid cell hypertrophy and hyperplasia in a dose-related and time-related manner. Furthermore, measurement of thyroid radioiodine uptake in vivo in rats confirmed that thiazole-Zn inhibited active iodide uptake into the thyroid, which reduced circulating levels of

serum T3 and T4. Decreases in circulating THs resulted in a compensatory increase in serum TSH levels through a negative feedback system. Subsequently, sustained excessive stimulation of the thyroid gland by TSH led to thyroid follicular cell hypertrophy and hyperplasia. In addition, thiazole-Zn increased sodium/iodide symporter (NIS) expression in the rat thyroid, and the increased NIS expression promoted and restored iodide uptake into the thyroids of rats. The risk of iodine intake inhibition by thiazole-Zn to humans, especially susceptible individuals, such as children and pregnant women, warrants additional attention.

- Lisco G, De Tullio A, Giagulli VA, De Pergola G, Triggiani V.

Interference on Iodine Uptake and Human Thyroid Function by Perchlorate-Contaminated Water and Food. *Nutrients*. 2020 12(6):1669. doi: 10.3390/nu12061669.

Background: Perchlorate-induced sodium-iodide symporter (NIS) interference is a well-recognized thyroid disrupting mechanism. It is unclear, however, whether a chronic low-dose exposure to perchlorate delivered by food and drinks may cause thyroid dysfunction in the long term. Thus, the aim of this review was to overview and summarize literature results in order to clarify this issue.

Methods: Authors searched PubMed/MEDLINE, Scopus, Web of Science, institutional websites and Google until April 2020 for relevant information about the fundamental mechanism of the thyroid NIS interference induced by orally consumed perchlorate compounds and its clinical consequences.

Results: Food and drinking water should be considered relevant sources of perchlorate. Despite some controversies, cross-sectional studies demonstrated that perchlorate exposure affects thyroid hormone synthesis in infants, adolescents and adults, particularly in the case of underlying thyroid diseases and iodine insufficiency. An exaggerated exposure to perchlorate during pregnancy leads to a worse neurocognitive and behavioral development outcome in infants, regardless of maternal thyroid hormone levels.

Discussion and conclusion: The effects of a chronic low-dose perchlorate exposure on thyroid homeostasis remain still unclear, leading to concerns especially for highly sensitive patients. Specific studies are needed to clarify this issue, aiming to better define strategies of detection and prevention.

- Villanger GD, Drover SSM, Nethery RC, Thomsen C, Sakhi AK, Øvergaard KR, Zeiner P, Hoppin JA, Reichborn-Kjennerud T, Aase H, Engel SM.

Associations between urine phthalate metabolites and thyroid function in pregnant women and the influence of iodine status. *Environ Int*. 2020 137: 105509. doi: 10.1016/j.envint.2020.105509.

Background: Human populations, including susceptible subpopulations such as pregnant women and their fetuses, are continuously exposed to phthalates. Phthalates may affect the thyroid hormone system, causing concern for pregnancy health, birth outcomes and child development. Few studies have investigated the joint effect of phthalates on thyroid function in pregnant women, although they are present as a mixture with highly inter-correlated

compounds. Additionally, no studies have investigated if the key nutrient for thyroid health, iodine, modifies these relationships.

Methods: In this study, we examined the cross-sectional relationships between concentrations of 12 urinary phthalate metabolites and 6 plasma thyroid function biomarkers measured mid-pregnancy (~17 week gestation) in pregnant women (N = 1072), that were selected from a population-based prospective birth cohort, The Norwegian Mother, Father and Child Cohort study (MoBa). We investigated if the phthalate metabolite-thyroid function biomarker associations differed by iodine status by using a validated estimate of habitual dietary iodine intake based on a food frequency questionnaire from the 22nd gestation week. We accounted for the phthalate metabolite mixture by factor analyses, ultimately reducing the exposure into two uncorrelated factors. These factors were used as predictors in multivariable adjusted linear regression models with thyroid function biomarkers as the outcomes.

Results: Factor 1, which included high loadings for mono-iso-butyl phthalate (MiBP), mono-n-butyl phthalate (MnBP), and monobenzyl phthalate (MBzP), was associated with increased total triiodothyronine (TT3) and free T3 index (fT3i). These associations appeared to be driven primarily by women with low iodine intake (<150 µg/day, ~70% of our sample). Iodine intake significantly modified (p-interaction < 0.05) the association of factor 1 with thyroid stimulating hormone (TSH), total thyroxine (TT4) and free T4 index (fT4i), such that only among women in the high iodine intake category (≥150 µg/day, i.e. sufficient) was this factor associated with increased TSH and decreased TT4 and fT4i, respectively. In contrast, factor 2, which included high loadings for di-2-ethylhexyl phthalate metabolites (ΣDEHP) and di-iso-nonyl phthalate metabolites (ΣDiNP), was associated with a decrease in TT3 and fT3i, which appeared fairly uniform across iodine intake categories.

Conclusion: We find that phthalate exposure is associated with thyroid function in mid-pregnancy among Norwegian women, and that iodine intake, which is essential for thyroid health, could influence some of these relationships.

- Wang Y, Xu P, Chang J, Li W, Yang L, Tian H.

Unraveling the toxic effects of neonicotinoid insecticides on the thyroid endocrine system of lizards. *Environ Pollut.* 2020 258: 113731. doi: 10.1016/j.envpol.2019.113731

The widespread use of neonicotinoids has resulted in large residues in the soil, which has a major impact on the lizards that inhabit the soil. Thyroid hormones play an important role in the growth and development of lizards. In this report, we assessed the disrupting effects of thyroid system on lizards after 28 days of continuous exposure to dinotefuran, thiamethoxam, and imidacloprid, respectively. Neonicotinoid insecticides could seriously affect the concentration of T4 in lizard plasma and the conversion of T4 to T3 in the thyroid gland. Specifically, exposure to dinotefuran affected the intake and utilization of iodine in the thyroid gland, resulting in insufficient thyroid function, which in turn lead to thyroid epithelial hyperplasia and follicular volume enlargement by negative feedback. Exposure to thiamethoxam could activate thyroid function, significantly increasing plasma T3 and T4 concentrations and promoting the binding of T3 and thyroid hormone receptors. Imidacloprid exposure could inhibit the secretion of thyroid hormones, leading to down-regulation of

thyroid hormone receptors and related phase II metabolic enzyme genes. This study verified that the continuous exposure of neonicotinoids could affect the lizard thyroid endocrine system. The harm of neonicotinoids to reptiles deserved more attention.

- Demeneix BA.

Evidence for Prenatal Exposure to Thyroid Disruptors and Adverse Effects on Brain Development. *Eur Thyroid J.* 2019: 283-292.

Thyroid hormone regulates vital processes in early brain development such as neuronal stem cell proliferation, migration, and myelination. The fetal thyroid is not fully functional until mid-pregnancy (18-20 weeks), so placental transfer of maternal thyroid hormones during early pregnancy is crucial, as is the maternal iodine status. The volume of chemical production has increased 300-fold since the 1970s. Thus, chemical exposure is ubiquitous; every child born today has dozens of man-made xenobiotic compounds in its blood. Increasing evidence from both epidemiological and animal or in vitro studies demonstrates that many of these chemicals have the potential to interfere with thyroid hormone availability and action at different physiological levels. These chemicals are found in numerous consumer products and include certain plastics, pesticides, perfluorinated compounds, and flame retardants. The last decades have seen exponential increases in neurodevelopmental disease including autism spectrum disorder and attention deficit/hyperactivity disorder. We hypothesize that prenatal exposure to mixtures of thyroid hormone-disrupting chemicals, with iodine deficiency potentially exacerbating the situation, has a strong probability of contributing to this increased incidence of neurodevelopmental disease, but could also entail a surreptitious, but socio-economically consequential, loss of IQ. Thyroid hormone receptor actions can modulate gene transcription, most often through epigenetic mechanisms. Thus, interference with epigenetic regulations is increasingly thought to link neurodevelopmental disease and IQ loss to thyroid hormone disruption.

- Duan J, Kang J, Deng T, Yang X, Chen M.

Exposure to DBP and High Iodine Aggravates Autoimmune Thyroid Disease Through Increasing the Levels of IL-17 and Thyroid-Binding Globulin in Wistar Rats. *Toxicol Sci.* 2018 163: 196-205.

Autoimmune thyroid disease (AITD) is the most common autoimmune disease that causes hypothyroidism. High iodine is a well-known factor that can induce thyroid disorders, including Hashimoto's thyroiditis, one of the main types of AITD. Recent epidemiological studies have indicated that phthalates, especially di-n-butyl phthalate (DBP) may induce thyroid disease. In this study, we aim to determine the effects and underlying mechanisms of high iodine and/or DBP exposure on AITD. Female Wistar rats were modeled with thyroglobulin and exposed to high iodine and/or DBP. We investigated histopathological changes in the thyroid and measured thyroid hormone levels in serum to assess thyroid function. In the thyroid and liver, we detected oxidative stress, proinflammatory factors (IL-1 β , IL-6, and IL-17) and the activation of activator protein 1 (AP-1), a transcription factor that is related to the synthesis of the thyroxine-binding globulin (TBG) and the activation of Th17. After blocking AP-1 with SP600125, we detected TBG and the Th17 related cytokines (IL-6 and IL-17). The data showed that thyroid damage and the alteration of thyroid hormones were greater when the rats were

exposed to both high iodine and DBP. Coexposure to DBP and high iodine enhanced the activation of AP-1 in the liver and thyroid, and induced an increase in the levels of TBG in serum and IL-17 in the thyroid. Blocking AP-1 activation prevented the increase of TBG and IL-17. The results indicate that high iodine and/or DBP exposure exacerbated AITD through altering TBG levels in serum and aggravating IL-17 in the thyroid.

- Medda E, Santini F, De Angelis S, Franzellin F, Fiumalbi C, Perico A, Gilardi E, Mechi MT, Marsili A, Citroni A, Leandri A, Mantovani A, Vitti P, Olivieri A.

Iodine nutritional status and thyroid effects of exposure to ethylenedithiocarbamates. *Environ Res.* 2017 154: 152-159. doi: 10.1016/j.envres.2016.12.019

Introduction: Italy is still characterized by a mild iodine deficiency and is among the most intensive users of chemical products for agriculture in Europe. The aim of this study was i) to evaluate thyroid effects of exposure to mancozeb, a fungicide widely used in agriculture, in a sample of Italian grapevine workers, and ii) to verify whether the iodine intake may modulate the risk of thyroid disruption due to the mancozeb metabolite ethylenthiourea (ETU).

Methods: One hundred seventy-seven occupationally exposed male workers (29 from Chianti, a mild iodine deficient area, and 148 from Bolzano an iodine sufficient province) and 74 non-occupationally exposed male controls (34 from Chianti and 40 from Bolzano) were enrolled in the study. Serum biomarkers of thyroid function, as well as urinary iodine and ETU concentrations were assessed. Moreover all the recruited subjects underwent clinical examination and thyroid ultrasound.

Results: Multivariate comparisons showed lower mean serum levels of FT4 in Chianti-workers as compared to Bolzano-workers. Moreover, an increased urinary iodine excretion ($>250\mu\text{g/L}$) was more frequently found among more exposed workers ($\text{ETU}>20\mu\text{g/L}$) than among less exposed ones and this effect was more pronounced in Chianti- than in Bolzano-workers. Chianti-workers also showed a significantly higher frequency of very low thyroid volume ($\leq 6.0\text{ml}$) as compared to controls.

Conclusions: These findings showed a mild thyroid disrupting effect due to occupational exposure to mancozeb, more pronounced in workers residing in an area characterized by a mild to moderate iodine deficiency as compared to workers residing in an area covered by a long-lasting iodine prophylaxis program.

- Zhang J, Zhang X, Li Y, Zhou Z, Wu C, Liu Z, Hao L, Fan S, Jiang F, Xie Y, Jiang L.

Low dose of Bisphenol A enhance the susceptibility of thyroid carcinoma stimulated by DHPN and iodine excess in F344 rats. *Oncotarget.* 2017 8: 69874-69887. doi: 10.18632/oncotarget.19434.

Thyroid carcinoma (TC) is the most common endocrine neoplasm. The risk of TC as a second primary malignancy (SPM) of breast cancer is significantly increased. Bisphenol A (BPA) is a widely contacted xenoestrogen and increases susceptibility to breast cancer through binding to

estrogen receptor alpha (ER α). However, the effect of BPA on thyroid carcinogenesis has not been fully demonstrated. This present study aimed to characterize the effects of BPA on the development of TC using a Fischer 344 (F344) rat model. In this study, we established a TC model using female F344 rats pretreated with N-Bis (2-hydroxypropyl) nitrosamine (DHPN) at a single dose of 2800 mg/kg (the DA group) or without DHPN (the DN group), followed by stimulation with BPA at the level of 250 μ g/kg (BPA250) or 1000 μ g/kg (BPA1000) and a basic diet containing potassium iodine (KI, 1000 μ g/L) for 64 weeks. We demonstrated that the incidence of TC in the BPA250 + KI of DA groups reached the highest at 50%, the incidence of thyroid hyperplasia lesions (including both tumors and focal hyperplasia lesions) in the BPA1000 + KI of DA groups reached 100% ($P < 0.05$). ER α protein and immunochemistry expression was upregulated in the BPA-exposed groups and the immunochemistry scores were positively correlated with PCNA. Thus, the present results indicate that BPA could enhance the susceptibility to TC stimulated by DHPN and iodine excess. ER α is probably involved in the proliferation effect of BPA. BPA or KI alone could not increase TC incidence.

- Zhou Z, Zhang J, Jiang F, Xie Y, Zhang X, Jiang L.

Higher urinary bisphenol A concentration and excessive iodine intake are associated with nodular goiter and papillary thyroid carcinoma. *Biosci Rep.* 2017; 37: BSR20170678.

In the present study, we investigated whether bisphenol A (BPA) levels and excessive iodine intake were associated with papillary thyroid carcinoma (PTC) and nodular goiter (NG). We determined total BPA concentrations (TBC) in paired serum and urine samples, and urinary iodine concentrations (UIC) in urine samples collected from PTC patients, NG patients, and healthy individuals, then compared BPA concentrations and UIC within and between each patient group. The results showed that there were no gender-specific differences in serum TBC and UIC in each group, and no differences across all patient groups. Urinary BPA concentrations (UBC) were higher in the NG and PTC groups compared with the control group. UBC showed gender-specific differences in the NG and PTC group. Furthermore, UIC were higher in the NG and PTC groups compared with the control group. Higher UBC and excessive iodine intake were risk factors for NG and PTC according to multivariate logistic regression analysis. There was a significant correlation between UBC and UIC in each group. These data suggested that higher UBC and excessive iodine intake are associated with NG and PTC. The metabolic and functional pathways between BPA and iodine are potentially linked to the pathogenesis and progression of NG and PTC.

- Mortensen ME, Birch R, Wong LY, Valentin-Blasini L, Boyle EB, Caldwell KL, Merrill LS, Moye J Jr, Blount BC.

Thyroid antagonists and thyroid indicators in U.S. pregnant women in the Vanguard Study of the National Children's Study.

Environ Res. 2016 149: 179-188. doi: 10.1016/j.envres.2016.05.017.

The sodium iodide-symporter (NIS) mediates uptake of iodide into thyroid follicular cells. This key step in thyroid hormone synthesis is inhibited by perchlorate, thiocyanate (SCN) and nitrate (NO $_3$) anions. When these exposures occur during pregnancy the resulting decreases in thyroid hormones may adversely affect neurodevelopment of the human fetus. Our objectives were to

describe and examine the relationship of these anions to the serum thyroid indicators, thyroid stimulating hormone (TSH) and free thyroxine (FT₄), in third trimester women from the initial Vanguard Study of the National Children's Study (NCS); and to compare urine perchlorate results with those in pregnant women from the National Health and Nutritional Examination Survey (NHANES). Urinary perchlorate, SCN, NO₃, and iodine, serum TSH, FT₄, and cotinine were measured and a food frequency questionnaire (FFQ) was administered to pregnant women enrolled in the initial Vanguard Study. We used multiple regression models of FT₄ and TSH that included perchlorate equivalent concentration (PEC, which estimates combined inhibitory effects of the anions perchlorate, SCN, and NO₃ on the NIS). We used multiple regression to model predictors of each urinary anion, using FFQ results, drinking water source, season of year, smoking status, and demographic characteristics. Descriptive statistics were calculated for pregnant women in NHANES 2001-2012. The geometric mean (GM) for urinary perchlorate was 4.04µg/L, for TSH 1.46mIU/L, and the arithmetic mean for FT₄ 1.11ng/dL in 359 NCS women. In 330 women with completed FFQs, consumption of leafy greens, winter season, and Hispanic ethnicity were significant predictors of higher urinary perchlorate, which differed significantly by study site and primary drinking water source, and bottled water was associated with higher urinary perchlorate compared to filtered tap water. Leafy greens consumption was associated with higher urinary NO₃ and higher urinary SCN. There was no association between urinary perchlorate or PEC and TSH or FT₄, even for women with urinary iodine <100µg/L. GM urinary perchlorate concentrations in the full sample (n=494) of third trimester NCS women (4.03µg/L) were similar to pregnant women in NHANES (3.58µg/L).

- Tonstad S, Jaceldo-Siegl K, Messina M, Haddad E, Fraser GE.

The association between soya consumption and serum thyroid-stimulating hormone concentrations in the Adventist Health Study-2. *Public Health Nutr.* 2016 19: 1464-70. doi:10.1017/S1368980015002943.

Objective: Consumers may choose soya foods as healthful alternatives to animal products, but concern has arisen that eating large amounts of soya may adversely affect thyroid function. The present study aimed to examine the association between soya food consumption and serum thyroid-stimulating hormone (TSH) concentrations in North American churchgoers belonging to the Seventh-day Adventist denomination that encourages vegetarianism.

Design: Participants completed six repeated 24 h dietary recalls within a 6-month period. Soya protein and soya isoflavone intakes were estimated, and their relationships to TSH concentrations measured at the end of 6 months were calculated using logistic regression analyses.

Setting: Calibration sub-study of the Adventist Health Study-2.

Subjects: Women (n 548) and men (n 295) who were not taking thyroid medications.

Results: In men, age and urinary iodine concentrations were associated with high serum TSH concentrations (>5 mIU/l), while among women White ethnicity was associated with high TSH. In multivariate models adjusted for age, ethnicity and urinary iodine, soya isoflavone and protein intakes were not associated with high TSH in men. In women higher soya isoflavone consumption was associated with higher TSH, with an adjusted odds ratio (highest v. lowest

quintile) of 4.17 (95 % CI 1.73, 10.06). Likewise, women with high consumption of soya protein (midpoint of highest quintile, 11 g/d) v. low consumption (midpoint of lowest quintile, 0 g/d) carried increased odds of high TSH (OR=2.69; 95 % CI 1.34, 5.30).

Conclusions: In women high consumption of soya was associated with elevated TSH concentrations. No associations between soya intake and TSH were found in men.

- Brucker-Davis F, Ganier-Chauliac F, Gal J, Panaïa-Ferrari P, Pacini P, Fénichel P, Hiéronimus S.

Neurotoxicant exposure during pregnancy is a confounder for assessment of iodine supplementation on neurodevelopment outcome. *Neurotoxicol Teratol.* 2015 51: 45-51. doi: 10.1016/j.ntt.2015.07.009.

Context: The developing brain is vulnerable to iodine deficiency (ID) and environmental neuro-toxicants.

Objectives: To assess neurocognitive development of children whose mothers have received (or not) iodine supplementation during pregnancy, in an area of borderline ID, while assessing in utero exposure to environmental neuro-toxicants.

Design/patients: Among 86 children born from normal euthyroid women who participated in our prospective interventional study on iodine supplementation (150 µg/day) started early in pregnancy, 44 (19 with iodine supplementation, 25 controls) were assessed at two years using the Bayley test. Information on parents' education and habits (smoking), and on child development was recorded. Thyroid tests at each trimester of pregnancy and on cord blood (CB) were available, as well as milk concentrations of selected environmental compounds known for their neurotoxicity, including heavy metals and PCBs.

Results: There was no difference in Bayley tests for children born to mothers with and without iodine supplementation, but sample size was small. Language and Social-Emotional Scales were negatively correlated with TBG at all times tested, while PCB 118 correlated negatively with all Language scales. Among maternal and CB thyroid tests, only CB thyroglobulin, the best marker of iodine status, correlated (negatively) with neurodevelopment scales (Motor and Expressive Language).

Conclusions: This pilot study suggests that PCB118 has a negative impact on neurocognitive development, possibly mitigating the benefit of iodine supplementation in an area of borderline ID. We propose that exposure to environmental neurotoxicants should be taken into account when designing studies on the benefit of iodine supplementation in pregnancy. The potential interactions between TBG, environmental neurotoxicants and brain development warrant further studies.

- Wang N, Zhou Y, Fu C, Wang H, Huang P, Wang B, Su M, Jiang F, Fang H, Zhao Q, Chen Y, Jiang Q.

Influence of Bisphenol A on Thyroid Volume and Structure Independent of Iodine in School Children. *PLoS One.* 2015 10(10):e0141248. doi: 10.1371/journal.pone.0141248.

Background: Although several studies have evaluated the relationship between bisphenol A (BPA) and thyroid functions, their results are not entirely consistent. Little is known about BPA in relation to thyroid volume and structure.

Methods: We examined the association of BPA with thyroid volume and thyroid nodules using data from 718 Chinese children living in the East Coast of China in 2012. First morning urine samples were collected for the determination of urinary BPA, creatinine, and urinary iodine concentrations (UIC). Thyroid volume (TV) and nodules were assessed by thyroid ultrasonography.

Results: The median of TV was 3.14ml. 459(63.9%) children took iodized salt at home and the median of UIC was 159µg/l. BPA was detected in 99.9% of the urine samples and the medians for boys and girls were 2.64 and 2.35µg/g creatinine, respectively. Of all participants 14.0% had thyroid nodules. Urinary BPA concentration was inversely associated with thyroid volume ($\beta = -0.033$, 95% CI: -0.053, -0.013) and the risk for multiple nodules (OR = 0.78; 95% CI: 0.63, 0.97). The associations above were similar for children who consumed iodized salt and those consumed non-iodized salt.

Conclusions: The data suggest that BPA may be one of the influencing factors for TV and thyroid nodules and its effects are independent of iodine nutrition status in children.

- Charatcharoenwitthaya N, Ongphiphadhanakul B, Pearce EN, Somprasit C, Chanthasenanont A, He X, Chailurkit L, Braverman LE.
The association between perchlorate and thiocyanate exposure and thyroid function in first-trimester pregnant Thai women. *J Clin Endocrinol Metab.* 2014 99: 2365-71. doi:10.1210/jc.2013-3986.

Context: Thyroid hormone is critical for fetal neurodevelopment. Perchlorate and thiocyanate decrease thyroidal iodine uptake by competitively inhibiting the sodium/iodide symporter. It is clear that perchlorate and thiocyanate anions can influence thyroid function. However, as pollutants in the environment, their impact is conflicting.

Objective: The objective was to determine the effects of environmental perchlorate and/or thiocyanate exposure on thyroid function in first-trimester pregnant women.

Design and patients: A cross-sectional study was conducted in 200 pregnant Thai women with a gestational age of 14 weeks or less.

Measures: Urinary iodide, perchlorate, thiocyanate, and serum thyroid function tests were measured.

Results: The women were aged 28.6 ± 6.1 years and the mean gestational age was 9.6 ± 2.7 weeks. Median urinary iodide, perchlorate, and thiocyanate concentrations were 153.5 µg/L, 1.9 µg/L, and 510.5 µg/L, respectively. Using Spearman's rank correlation analyses, there were positive correlations between serum TSH and urine perchlorate to creatinine ($r = 0.20$, $P = .005$) and TSH and thiocyanate to creatinine ratios ($r = 0.22$, $P = .001$). There were negative

correlations between free T4 and the perchlorate to creatinine ratio ($r = -0.18$, $P = .01$) and free T4 and the thiocyanate to creatinine ratio ($r = -0.19$, $P = .008$). In multivariate analyses adjusting for log thiocyanate to creatinine ratio, log iodide to creatinine ratio, and gestational age, log perchlorate to creatinine ratio was positively associated with log TSH ($P = .002$) and inversely associated with log free T4 ($P = .002$). Log thiocyanate to creatinine ratio was a significant positive predictor of log TSH ($P = .02$) in women with a urine iodide level of less than 100 $\mu\text{g/L}$.

Conclusions: Low-level environmental exposure to perchlorate and thiocyanate is common in Thailand. Low-level exposure to perchlorate is positively associated with TSH and negatively associated with free T4 in first-trimester pregnant women using multivariate analyses. In multivariate analyses, thiocyanate exposure is also positively associated with TSH in a subgroup of pregnant women with low iodine excretion.

- European Food Safety Authority. Panel on Contaminants in the Food Chain, 2014.

Scientific Opinion on the risks to public health related to the presence of perchlorate in food, in particular fruits and vegetables. *EFSA Journal* 2014; 12(10):3869, 117 pp. doi:10.2903/j.efsa.2014.3869

The European Food Safety Authority (EFSA) received a request from the European Commission for a scientific opinion on perchlorate in food, in particular fruits and vegetables. Perchlorate is a contaminant released into the environment from both natural and anthropogenic sources. The use of natural fertilisers and perchlorate contaminated irrigation water may lead to substantial concentrations in leafy vegetables. Water disinfection with chlorinated substances that potentially degrade to perchlorate could be another potential source of contamination. EFSA received analytical results for 11 675 samples submitted by eight Member States, mainly for fruits, vegetables, and fruit and vegetable products. The EFSA Panel on Contaminants in the Food Chain (CONTAM Panel) performed estimates of both chronic and 'short-term' exposure considering the available dataset, and data from the literature on the levels of perchlorate in fruit juices, alcoholic beverages, milk, infant formulae and breast milk. The CONTAM Panel established a tolerable daily intake of 0.3 $\mu\text{g/kg}$ body weight per day, based on the inhibition of thyroid iodine uptake in healthy adults. Amongst the vulnerable subpopulations, potential acute effects of perchlorate have been suggested for fetuses and infants. The CONTAM Panel noted that a single acute exposure to perchlorate at levels found in food and water is unlikely to cause adverse effects on human health, including the more vulnerable groups of the population, and concluded that the establishment of an acute reference dose for perchlorate is not warranted. Overall, the CONTAM Panel concluded that the chronic dietary exposure to perchlorate is of potential concern, in particular for the high consumers in the younger age groups of the population with mild to moderate iodine deficiency. Furthermore, it is possible that exposure to perchlorate is of concern for infants breast-fed by iodine-deficient mothers.

- Suh M, Abraham L, Hixon JG, Proctor DM.

The effects of perchlorate, nitrate, and thiocyanate on free thyroxine for potentially sensitive subpopulations of the 2001-2002 and 2007-2008 National Health and Nutrition Examination Surveys. *J Expo Sci Environ Epidemiol.* 2014 24: 579-87. doi: 10.1038/jes.2013.67.

Among women with urinary iodine concentration $<100 \mu\text{g/l}$ in the 2001-2002 National Health and Nutrition Examination Survey (NHANES), urinary perchlorate was associated with significant changes in thyroid stimulating hormone and total thyroxine (T₄). Although perchlorate, nitrate, and thiocyanate all potentially act to inhibit iodide uptake, free T₄ was not found to be associated with exposure to these chemicals in the same data. Fetuses of pregnant mothers with iodine deficiency are thought to be a sensitive subpopulation for perchlorate exposure, but the potential associations between free T₄ and exposure to these chemicals among pregnant mothers in NHANES 2001-2002 and 2007-2008 have not been specifically evaluated to date. This study investigates the potential associations between urinary perchlorate, nitrate, and thiocyanate and serum free T₄ in individuals with low urinary iodine levels and pregnant women. Multivariate regression models of free T₄ were conducted and included urinary perchlorate, nitrate, thiocyanate, and covariates known to have an impact on the thyroid (anti-thyroid peroxidase (TPO) antibodies, age, race/ethnicity, body mass index, and hours of fasting). Meta-analyses were also conducted on non-pregnant and on pregnant women from the two survey cycles. Urinary nitrate was associated with serum free T₄ in non-pregnant women of NHANES 2001-2002 who had urinary iodine $\geq 100 \mu\text{g/l}$. In the meta-analysis, urinary perchlorate, nitrate, and thiocyanate were significant predictors of serum free T₄ in non-pregnant women. No association was found in men and pregnant women. TPO antibodies were significant predictors of free T₄ among non-pregnant women only when the models included urinary perchlorate, nitrate, or thiocyanate. Risk assessment for perchlorate exposure should consider co-exposure to nitrate and thiocyanate.

- Hisada A, Shimodaira K, Okai T, Watanabe K, Takemori H, Takasuga T, Noda Y, Shirakawa M, Kato N, Yoshinaga J. **Serum levels of hydroxylated PCBs, PCBs and thyroid hormone measures of Japanese pregnant women.** *Environ Health Prev Med.* 2013; 18:205-14. doi: 10.1007/s12199-012-0306-6.

Objectives: The purpose of this study was to investigate the associations between serum concentrations of hydroxylated PCBs (OH-PCBs) and PCBs and measures of thyroid hormone status of Japanese pregnant women.

Methods: The concentrations of free thyroxine (fT₄), thyroid stimulating hormone (TSH), and thyroxine binding globulin (TBG) as well as 16 OH-PCB isomers and 29 PCB isomers were analyzed in the serum of 129 women sampled in the first trimester of gestation. Dietary and lifestyle information of the subjects was obtained by self-administered questionnaire. Multiple regression analysis was performed using measures of thyroid hormones as the dependent variable and serum levels of OH-PCBs/PCBs, urinary iodine concentration, and other potential covariates (age, BMI, smoking, etc.) as independent variables.

Results: Geometric mean (GM) concentration of the sum of 16 isomers of OH-PCBs was 120 pg/g wet wt. and that of 29 isomers of PCBs was 68 ng/g lipid wt., respectively, in the serum of the subjects. Iodine nutrition was considered adequate to high from urinary iodine level (GM, 370 $\mu\text{g/g}$ creatinine). The mean concentration of TSH, fT₄ and TBG was $1.34 \pm 1.37 \mu\text{IU/mL}$, $1.22 \pm 0.16 \text{ ng/dL}$ and $33.0 \pm 6.4 \mu\text{g/mL}$, respectively, with a small number of subjects who were outside the reference range. Multiple regression analysis revealed that serum concentrations of OH-PCBs/PCBs were not significantly associated with any of the measures of

thyroid hormone status.

Conclusions: Exposure/body burden of OH-PCBs and PCBs at environmental levels does not have a measurable effect on thyroid hormones.

- Tran L, Hammuda M, Wood C, Xiao CW.

Soy extracts suppressed iodine uptake and stimulated the production of autoimmunogen in rat thyrocytes. *Exp Biol Med (Maywood)*. 2013 238: 623-30.

Soy consumption is associated with thyroid disorders such as hypothyroidism, goiter, and autoimmune thyroid disease (ATD) as well as increased iodine requirement in certain cases. However, the anti-thyroid component(s) in soy are yet to be identified and the molecular mechanism(s) involved remain unclear. This study examined the effects of soy isoflavones (ISF) on iodide uptake and expression of thyroglobulin (Tg) and sodium/iodide symporter (NIS) in thyrocytes. Fischer rat thyroid cells (FRTL) were treated with Novasoy (a soy alcohol extract containing 30% ISF) or major ISF aglycones or glycosides for 24 h. Iodide uptake was measured by a colorimetric assay. The protein level of Tg and NIS was measured by Western blotting. Cytotoxicity of tested compounds was determined by the MTT cell proliferation assay. Iodide uptake in FRTL cells was dose-dependently suppressed by Novasoy added into the cell culture (10, 25, or 50 µg/mL, $P < 0.05$). However, neither the major ISF aglycones nor glycosides alone or in combination had similar effects. Novasoy (up to 200 µg/mL) had no cytotoxic effect. Novasoy (1, 10, and 50 µg/mL) and genistein (1 and 10 µM) markedly increased the protein content of a 40 kDa Tg fragment (P40, a known autoimmunogen) and non-glycosylated NIS in the FRTL cells ($P < 0.05$). Overall, this study demonstrated that the alcohol soluble component(s) other than the major ISF in soy remarkably inhibited iodide uptake in the FRTL cells. Soy ISF, particularly genistein, induced the production of P40, which might be responsible for the higher incidence of ATD reported in soy infant formula-fed children.

- Langer P, Tajtakova M, Kocan A, Drobna B, Kostalova L, Fodor G, Klimes I.

Thyroid volume, iodine intake, autoimmune thyroid disorders, inborn factors, and endocrine disruptors: twenty-year studies of multiple effects puzzle in Slovakia. *Endocr Regul*. 2012 46:191-203. doi: 10.4149/endo_2012_04_191.

Objective: The aim of this study was to evaluate multiple interrelations between several endogenous and exogenous effects and the thyroid volume and function in large groups of children, adolescents, and adults with a sufficient whole life intake of the iodine.

Subjects and methods: The data were obtained either by cross sectioned or longitudinal studies in a total of 4998 children and adolescents (aged 7 to 17 years) and 2501 adults (1071 males and 1430 females aged 20-75 years). Thyroid volume (ThV) was measured by ultrasound, antibodies, and hormones by electrochemiluminiscent immunoassay, and endocrine disruptors (EDs, polychlorinated biphenyls-PCB, dichlorodiethyl-ichloroethylene-DDE, and hexachlorobenzene-HCB) by high resolution gas chromatography/mass spectrometry.

Results: 1. In large groups of boys and girls of age 7, 10, 13 or 17 years, the ThV was significantly higher in the 10th decile than in pooled nine lower deciles. Moreover, in 17-year old subjects

significantly higher prevalence of hypoechogenicity by ultrasound, positive thyroperoxidase antibodies (TPOab), and increased thyrotropin (TSH) levels were found in the 10th decile. 2. In a small group of children, some individuals revealed consistently higher ThV during the whole 7-year follow-up period irrespective of supplementation with iodine. 3. In 325 sibling pairs of age 10-19 years, born within three years, three groups with different ThV/m² of body surface were distinguished: Group A (183 pairs having both ThVs small), Group B (103 pairs having both ThVs large); Group C (33 pairs having one ThV small and the other one large). Similar aggregation of ThVs in three groups was observed in 13 pairs of discordant twins and 19 sibling triads in which all the siblings were born within four years. 4. In 42 concordant twins, several pairs had ThV nearly twice as high (in terms of both plain ThV or ThV/m² of the body surface) as several other pairs of the same age which is assumed to be a result of a genetic background. 5. In large cohorts of males and females, a highly significant positive correlation was found between the ThV and high level of TPOab on one side and EDs on the other side. However, in nearly the same numbers of subjects with low TPOab, negative correlation was seen between ThV and disruptors. These observations may apparently support the synergic effect of the autoimmunity and EDs on the thyroid function.

Conclusions: Several cases of an excessive thyroid growth in the iodine replenished children, adolescents, and adults may apparently result from the autoimmune thyroiditis, probably induced by immunogenic action of iodine in presumably disposed individuals. However, in some cases even simultaneous participation of EDs can not be excluded. Some observations have also suggested that excessive thyroid growth in the iodine replenished adolescent and adult population which was equally exposed to disruptors may also result from other reasons as the unfavorable hereditary background.

- Leung AM, Braverman LE, He X, Schuller KE, Roussilhes A, Jahreis KA, Pearce EN.

Environmental perchlorate and thiocyanate exposures and infant serum thyroid function. *Thyroid*. 2012 22: 938-43. doi: 10.1089/thy.2012.0058.

Background: Breastfed infants rely on maternal iodine for thyroid hormone production required for neurodevelopment. Dietary iodine among women of childbearing age in the United States may be insufficient. Perchlorate (competitive inhibitor of the sodium/iodide symporter [NIS]) exposure is ubiquitous. Thiocyanate, from cigarettes and diet, is a weaker NIS inhibitor. Environmental perchlorate and thiocyanate exposures could decrease breast milk iodine by competitively inhibiting NIS in lactating breasts (thus impairing infants' iodine availability), and/or infants' thyroidal NIS to directly decrease infant thyroid function. The current study assessed the relationships between environmental perchlorate and thiocyanate exposures and infant serum thyroid function.

Methods: Iodine, perchlorate, and thiocyanate in breast milk, maternal and infant urine, and infant serum thyroid function tests were cross-sectionally measured in Boston-area women and their 1-3 month-old breastfed infants. Univariate and multivariable analyses assessed relationships between iodine, perchlorate, thiocyanate, thyroid-stimulating hormone (TSH), and free thyroxine (FT₄) levels.

Results: In 64 mothers and infants, median (range) iodine levels were 45.6 µg/L (4.3-1080) in

breast milk, 101.9 µg/L (27-570) in maternal urine, and 197.5 µg/L (40-785) in infant urine. Median perchlorate concentrations were 4.4 µg/L (0.5-29.5) in breast milk, 3.1 µg/L (0.2-22.4) in maternal urine, and 4.7 µg/L (0.3-25.3) in infant urine. There were no correlations between infant TSH or FT4 and iodine, perchlorate, and thiocyanate levels in breast milk, maternal urine, and infant urine. In multivariable analyses, perchlorate and thiocyanate levels in breast milk, maternal urine, and infant urine were not significant predictors of infant TSH or FT4.

Conclusions: Boston-area mothers and their breastfed infants are generally iodine sufficient. Although environmental perchlorate and thiocyanate are ubiquitous, these results do not support the concern that maternal and infant environmental perchlorate and thiocyanate exposures affect infant thyroid function.

- Pearce EN, Alexiou M, Koukkou E, Braverman LE, He X, Ilias I, Alevizaki M, Markou KB.

Perchlorate and thiocyanate exposure and thyroid function in first-trimester pregnant women from Greece. Clin Endocrinol (Oxf). 2012 77:471-4. doi: 10.1111/j.1365-2265.2012.04407.x.

Objective: Thyroid hormone, requiring adequate maternal iodine intake, is critical for neurodevelopment in utero. Perchlorate and, less so, thiocyanate decrease uptake of iodine into the thyroid gland by competitively inhibiting the sodium/iodide symporter (NIS). It remains unclear whether environmental perchlorate exposure adversely affects thyroid function in first-trimester pregnant women.

Design: Cross-sectional.

Patients: 134 pregnant women from Athens, Greece, at mean \pm SD 10.9 \pm 2.3 weeks' gestation.

Measurements: Urinary iodide, perchlorate, and thiocyanate and thyroid function tests were measured.

Results: The median urinary iodide was 120 µg/l. Urinary perchlorate levels were detectable in all women: median (range) 4.1 (0.2-118.5) µg/l. Serum thyroperoxidase antibodies (TPO Ab) were detectable in 16% of women. Using Spearman's rank correlation analyses, there was no correlation between urinary perchlorate concentrations and serum TSH, although inverse correlations were seen between urine perchlorate and free T3 and free T4 values. In univariate analyses, urine thiocyanate was positively correlated with serum TSH, but was not associated with serum free T3 or free T4. Urine perchlorate was positively correlated with gestational age. In multivariate analyses adjusting for urinary iodide concentrations, urine thiocyanate, gestational age, maternal age and TPO Ab titres, urine perchlorate was not a significant predictor of thyroid function.

Conclusions: Low-level perchlorate and thiocyanate exposure is ubiquitous, but, in adjusted analyses, is not associated with alterations in thyroid function tests among mildly iodine-deficient Greek women in the first trimester of pregnancy.