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Perchlorate, iodine and the thyroid

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Abstract

In pharmacologic doses, perchlorate inhibits thyroidal iodine uptake and subsequently decreases thyroid hormone production. Although pharmacologic doses may be used in the treatment of hyperthyroidism, recent literature has focussed on the detection of low levels of perchlorate in the environment, groundwater and foodstuffs and their potential adverse effects on human thyroid function. This is of particular concern to the developing foetus and infant, whose normal neurodevelopment depends on adequate iodine intake for the production of thyroid hormones. Further research is needed to clarify the potential health effects of low-level chronic environmental perchlorate exposure. The health impact of environmental perchlorate may be dependent upon adequate iodine intake and should be interpreted in combination with other environmental exposures that are also potential thyroidal endocrine disruptors.

Keywords

perchlorate; iodine; thyroid; sodium-iodide symporter (NIS)

Perchlorate is an inorganic anion that is a potent competitive inhibitor of the sodium-iodide symporter (NIS) found on the basolateral membrane of thyroid cells. In pharmacological doses, perchlorate decreases the active transport of iodine into the thyroid. During the 1950s, perchlorate (in high doses of 600–1000 mg daily) was used to treat hyperthyroidism.[1,2] Its use diminished after several cases of aplastic anaemia were observed, perhaps due to the large doses employed.[3]

However, perchlorate use has recently regained some popularity. In the early 1980s, perchlorate doses of up to 900 mg daily, but usually far lower, were used for as long as 1 year for the treatment of Graves' disease without serious side effects.[4] Recently, lower doses have been used safely and effectively in the treatment of Graves' disease and iodine-induced hyperthyroidism.[5,6] Perchlorate has also been successful in transiently restoring euthyroidism in patients with amiodarone iodine-induced hypothyroidism by decreasing intrathyroidal iodine concentrations[7] and for prophylaxis against iodine-induced hyperthyroidism from the administration of iodinated contrast agents.[8] Although still in use

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in Europe and other regions, medicinal perchlorate is no longer readily available in the U.S. since the producer discontinued production owing to limited demand.

Environmental perchlorate comes from a variety of sources, is extremely stable as an inorganic salt and persists in low levels in soil and groundwater over long periods.[9] The question of whether low-level environmental perchlorate exposure has significant consequences for human health has generated considerable controversy. In this review, we summarise iodine nutrition and thyroid hormone production, environmental sources of perchlorate exposure, the effects of perchlorate on thyroid function, the major human assessments of perchlorate, potential impacts of perchlorate levels on vulnerable populations, recent issues surrounding perchlorate regulation and the current recommendations for iodine nutrition.

Iodine nutrition and thyroid hormone production

Concern about environmental perchlorate exposure centres on its inhibition of iodide uptake into the thyroid. Decreased iodine intake may decrease thyroid hormone production. Perchlorate exposure, therefore, might be particularly detrimental in iodine-deficient individuals. However, single measurements of urinary iodine cannot be used to determine iodine status in an individual, given the day-to-day variation in dietary iodine intake. Median urinary iodine levels are used instead and reflect dietary iodine sufficiency across populations.[10]

Iodine deficiency continues to be an important global public health issue, with an estimated 2.2 million people (38% of the world's population) living in iodine-deficient areas.[10] In 1990, the United Nations World Summit for Children set forth the goal of eliminating iodine deficiency worldwide[11], and considerable progress has since been achieved. This has largely been led by programmes of universal salt iodisation (USI) in various countries, in line with the recommendations of the World Health Organization (WHO).[12] However, many countries remain iodine deficient.[13,14] In the U.S., data from large population studies have shown that median urinary iodine levels decreased by approximately 50% between the early 1970s and the early 1990s, although the population overall remained iodine sufficient.[15] Subsequent studies have shown that this decrease has stabilised.[16]

Environmental sources of perchlorate exposure

Low-level perchlorate exposure appears to be ubiquitous. Perchlorate is produced by natural atmospheric processes[17] and has been measured in rainwater, snow[18] and groundwater.[19] Environmental perchlorate is highly soluble and extremely stable under normal atmospheric conditions.[20] Perchlorate samples from drinking water and groundwater held for up to 638 days can be recovered to within 95% of the original concentrations using ion chromatography.[21] A large area of natural perchlorate, co-existing with other substances that date back several thousands of years, was recently reported in the southwestern part of the U.S. and is presumed to have leached into surrounding groundwater.[22]

The use of perchlorate salts in various manufacturing industries in the past few decades, particularly in the western U.S., has contributed to its widespread presence at low levels. It

has been a by-product of industrial production of solid rocket fuel, road flares, fireworks, matches, and airbag inflation systems. High levels of perchlorate can also be found in some crop fertilisers exported from Chile[23], whose Atacama Desert region has high natural perchlorate levels.[24]

Following the development of sensitive measurement methods (e.g., ion chromatography and tandem mass spectrometry) in the late 1990s[25,26], low levels of perchlorate have been detected in various sources. In the U.S., it has been found in many substances, including tobacco, alfalfa, tomato, cow's milk[20], cucumber, lettuce, soybeans[27], eggs[28] and vitamins.[29] In 1998, the U.S. Environmental Protection Agency (EPA) added perchlorate to the Drinking Water Candidate Contaminant List.[30]

Perchlorate has also been detected in many other consumable products worldwide. In Japan, perchlorate was detectable in dairy milk in concentrations exceeding that of U.S. surveys.[31] In Canada, it has been found in a variety of fruits and vegetables, milk, tap and bottled water, wine and beer products.[32] A Chinese study reported perchlorate concentrations in rice, bottled water and milk from different regions.[33] Finally, perchlorate has been detected in the drinking water of India, although levels were lower than that of the U.S.[34]

Effects of perchlorate on thyroid function

In the normal thyroid, iodide is actively transported across the basolateral membrane of thyroid cells and used to produce thyroid hormone. Transport is achieved through the NIS by an energy-dependent mechanism. NIS has been cloned from the rat[35] and human[36] thyroid. Investigations have demonstrated that NIS activity is Na^+-dependent and electrogenic, and the stoichiometry of cotrans-port is 2 Na^+:1 anion.[37] NIS has been identified at the molecular level of some extrathyroidal tissues, such as the lactating mammary gland (where concentrating iodine would be useful to the breastfed infant), the salivary gland and gastric[38] and intestinal mucosae[39], areas where the physiological functions of iodide transport have yet to be elucidated.

Perchlorate competitively inhibits iodide at the level of the NIS with 30 times the affinity for iodide.[40] It is also actively transported by the NIS into the thyroid in a dose-dependent manner.[41,42] Perchlorate is not significantly metabolised in humans, and thus perchlorate exposure is best assessed by urinary levels.[17] During lactation, perchlorate exposure may also be assessed by breast milk concentrations.[17] Ion chromatography and tandem mass spectrometry are selective, sensitive and rapid methods for perchlorate measurements in human urine samples[43], blood[44] and breast milk.[45]

Studies of perchlorate exposure in healthy volunteers

Studies in the late 1990s reporting the prevalence of environmental perchlorate levels have since generated an interest in assessing human exposure risks. Following the detection of perchlorate in the groundwater of the southwestern U.S., we reported two studies assessing the effect of 3 mg and 10 mg of perchlorate daily (dissolved in spring water), respectively, for 14 days on thyroid function.[46,47] A significant decrease in thyroidal ^{123}I uptake on day 14 of perchlorate ingestion was observed with the 10-mg dose, an expected effect of

perchlorate on iodide transport. Neither perchlorate dose, both far higher than environmental exposures, affected serum thyroid function tests.

In a larger study, Greer et al. assessed the perchlorate dose response on the thyroidal ^{123}I uptake and thyroid function in 37 human subjects.[48] In these volunteers, drinking water with perchlorate concentrations at 0.007, 0.02, 0.1 or 0.5 mg kg $^{-1}$ per day was administered for 14 days. The investigators found no changes in thyroid function for doses up to 35 mg. However, a decrease of the thyroidal ^{123}I uptake was noted at the 1.4 mg per day dose (but not the 0.5 mg per day dose), thereby suggesting a no-effect level for perchlorate of 0.5 mg per day, which is far higher than typical environmental exposures.

These short-term studies were followed by a report on the effects of low-dose (placebo, 0.5 mg or 3.0 mg) perchlorate administered as part of a prospective, double-blinded, randomised trial of perchlorate to 13 healthy volunteers over 6 months. Similar to the results of the previous shorter-term studies, there were no changes in serum thyroid function tests and no effect on the thyroidal ^{123}I uptake in all dose groups[49], although this study was not adequately powered to assess these outcomes.

Occupational perchlorate exposure

The impact of perchlorate has also been studied in U.S. perchlorate production workers, a group whose exposure is longer term and at far higher exposure levels. A study at one production plant, which monitored perchlorate exposure by estimates of airborne contact, found no changes in thyroid function in the workers when assessed during or after shift work.[50] Another study by Lamm et al. in perchlorate production workers also demonstrated no changes in thyroid function among the four strata of workers with increasing doses of mean urinary perchlorate values.[51]

In the largest study of perchlorate exposure at a U.S. perchlorate production facility, 29 perchlorate workers were studied who had been exposed intermittently to high perchlorate levels over a median duration of 5.9 years.[52] Thyroidal iodide uptake was slightly decreased in the hours following overnight exposure, but serum thyroid function tests were not affected by this long-term, intermittent, high-level exposure to perchlorate, resulting in urine concentrations of 43 mg l $^{-1}$. The above studies of perchlorate exposure in healthy volunteers and perchlorate production workers have been recently summarised.[53,54]

Population studies of perchlorate exposure

In the 2001–2002 U.S. National Health and Examination Survey (NHANES), perchlorate was detected in all 2820 spot urine specimens (median urine perchlorate concentration 3.6 mg l $^{-1}$)[55] and was negatively associated with total thyroxine (T4) and positively associated with thyroid-stimulating hormone (TSH) values in women, primarily those with urine iodine concentrations <100 mg l $^{-1}$.[56] However, these relationships were not observed in men; in a follow-up subset analysis of this dataset (which analysed only women of childbearing age) using creatinine-adjusted urinary values[57]; nor in a large European study assessing the serum thyroid function of iodine-deficient pregnant women.[58] Some of the reasons for the inconsistent trends seen in these and the other studies were recently reviewed.[59] Additional

research is needed to clarify whether low-level perchlorate exposure truly affects thyroid function.

Perchlorate exposure during pregnancy

The unborn foetus and developing infant may be especially vulnerable to perchlorate exposure. Adequate iodine nutrition is needed for thyroid hormone synthesis, and thyroid hormone plays a vital role in foetal neurodevelopment *in utero*.[60] Maternal placental supply of T4 is the major contributor to foetal serum T4 levels in early pregnancy and plays a crucial role in infants' neurodevelopment *in utero*.[61] In a severely iodine-deficient area of China, maternal iodine supplementation in the third trimester and the immediate post-partum period resulted in improved brain growth and developmental achievements in their offspring.[60] In infancy, iodine deficiency may result in developmental delays, particularly in language and memory skills.[62] Maternal hypothyroidism, including subclinical disease, may lead to impaired neurological development and intelligence quotient (IQ) scores in their offspring.[63,64] Iodine deficiency remains the leading cause of preventable mental retardation worldwide.

During pregnancy, sufficient iodine nutrition is particularly important. Thyroid hormone requirements increase, particularly during the first trimester[65], due to higher concentrations of thyroxine-binding globulin, placental inner-ring deiodination of thyroxine to the inactive iodothyronine (reverse T3) and transfer of small amounts of thyroxine to the foetus, especially during the first trimester when foetal thyroid function is absent. In addition, the glomerular filtration rate and clearance of proteins and other molecules are both increased in pregnancy, thereby likely causing increased renal iodide clearance and a decreased circulating pool of plasma iodine.[66] Thus, although the foetal thyroid is capable of trapping iodide by about week 12 of gestation[67], high maternal perchlorate concentrations could potentially decrease thyroidal iodine available to the foetus by inhibiting placental NIS. Perchlorate and other environmental inhibitors of the NIS have been found in measurable quantities in human amniotic fluid.[68]

There are limited data regarding low-level environmental perchlorate exposure and maternal thyroid function during pregnancy. A Chilean study found no increases in TSH or decreases in free thyroxine or urinary iodine concentrations in pregnant women living in three areas (all of which had more than adequate mean urinary iodine levels) with long-term environmental perchlorate exposure.[69] A follow-up analysis of this cohort also confirmed the lack of association between individual urinary iodide or perchlorate concentrations and thyroid function in the pregnant women.[70] Our studies of large cohorts of first-trimester pregnant women from the U.S., Europe and Argentina found that environmental perchlorate exposure did not affect maternal thyroid function.[58,71,72]

The data assessing the effect of maternal perchlorate exposure in neonates and children and thyroid function remain unclear. Brechner et al. reported that newborns whose mothers resided in areas with high perchlorate levels in drinking water in U.S. had higher TSH values than those who did not[73], although a further analysis of these data showed that the differences were due to factors other than perchlorate exposure.[74] In one study of three cities

in northern Chile, perchlorate concentrations up to 120 μm $l^{—1}$ in drinking water were not associated with differences in serum TSH levels in newborn and school-age children.[75] The TSH values of neonates at age 1 month living in a U.S. region where perchlorate levels are up to 15 ppb in drinking water were not affected by environmental perchlorate exposure.[76] Similar findings were observed in another U.S. community where perchlorate was detected in groundwater wells.[77] In Israel, neonatal thyroxine levels were not affected by serum perchlorate levels far exceeding those of the U.S. EPA recommendations.[78]

Perchlorate exposure during lactation

Lactating women and their infants may also be particularly vulnerable to the thyroidal effects of environmental perchlorate exposure. Iodine is actively secreted into breast milk through NIS[79], and breastfed infants are completely reliant on adequate maternal dietary iodine intake.[80] Similar to its mechanism on thyroid cells, perchlorate is a competitive inhibitor of the NIS found on lactating breast cells.[41] Perchlorate transfer into breast milk may thus decrease breast milk iodine levels[81] and adversely affect infant thyroid hormone levels, either by decreasing iodine in breast milk or by directly affecting infants' thyroid hormone synthesis.

Recently, the U.S. Food and Drug Administration reported in a Total Diet Study that infants and children have the highest intakes of perchlorate by body weight based on estimated intake.[82] Measured breast milk iodine and perchlorate levels have been assessed only in a few small U.S. studies. Perchlorate has been detected in human breast milk ranging from 1.4 to 92.2 mg μl^{-1} (10.5 μg l^{-1}, mean) in 18 U.S. states[83] and 1.3 to 411 μg l^{-1} (9.1 μg l^{-1}, median) in the Boston, U.S. area.[84] Perchlorate has also been detected in human colostrum (the substance from the postpartum mammary gland prior to the production of breast milk) of 46 women in the Boston, U.S. area, ranging from < 0.05 to 187.2 μmol l^{-1}.[85]

Kirk et al. reported that the breast milk iodine content was inversely correlated with breast milk perchlorate concentrations in six women with breast milk perchlorate levels 10 μg l^{-1}.[83] This association was not observed in the 23 of 49 breast milk samples with perchlorate content 10 μg l^{-1} in a Boston-area cohort.[84] Breast milk perchlorate is known to have some temporal variability.[86] Using a model of parallel and competitive transport of perchlorate and iodine excretion in the urine and breast milk of lactating women, Dasgupta et al. have reported that 12 of 13 infants were ingesting inadequate iodine amounts in breast milk and that 9 of 13 infants were consuming perchlorate amounts above the upper limit proposed by the U.S. National Academy of Sciences.[87] An analysis of simulated perchlorate exposure also suggested that a majority of breastfed infants may be ingesting perchlorate levels in breast milk exceeding the U.S. EPA recommendations.[88]

Formula-fed babies may also be at risk for perchlorate exposure. Perchlorate levels of 0.22 to 4.1 μg l^{-1} (1.5 μg l^{-1}, median) were found in all 17 brands of the U.S. infant formula recently assessed[84], confirming previous data reporting perchlorate content in infant formula.[89] Infants consuming certain brands may be at risk for ingesting perchlorate amounts exceeding that of the U.S. EPA recommendations.[90]

Other environmental inhibitors of the sodium/iodide symporter

The effects of perchlorate on iodine availability should be interpreted in the context of other NIS inhibitors. These include thiocyanate, a metabolite of cyanide that is produced as a by-product of cigarette smoke and found in a large variety of foods, and nitrate, which is produced naturally. Comparatively, perchlorate is a very potent inhibitor of the NIS; its effects are 15-fold greater than thiocyanate, 30-fold compared to iodide, and 240-fold compared to nitrate.[40] Nonetheless, because exposure to thiocyanate and nitrate is ubiquitous, the additive effects on iodide uptake may be important when assessing iodine availability. Some have urged that the detection, concentrations and potencies of these other NIS inhibitors also be considered in studies reporting environmental perchlorate exposure[59], which were not assessed in the large U.S. population study reporting the adverse effects of perchlorate exposure on thyroid function in women.[56]

There are many other pathways by which environmental chemicals can disrupt thyroid function.[91–95] No studies to date have examined the additive effects of endocrine disruptors which affect the other aspects of thyroid hormone synthesis and metabolism.

Regulation of perchlorate exposure

There has been considerable debate regarding safe levels of perchlorate exposure. A reference (RfD) dose of 0.0007 mg kg $^{-1}$ per day of perchlorate was proposed in a 2005 U.S. National Academy of Sciences report.[96] This dose, which defines the estimate of a substance's daily human exposure that is likely to be without any appreciable lifetime effects,[97] was based primarily on the prospective study by Greer et al. of varying perchlorate doses administered to 37 adult volunteers.[48] This RfD dose is approximately equivalent to an EPA-defined Maximum Contaminant Level (MCL) of 24.5 ppb in drinking water based on standard estimates. The results of one investigation suggest that the current MCL threshold should pose little or no risk to the large majority of U.S. individuals, including pregnant women, based on various potential drinking water estimates.[98]

The potential health-related issues of environmental perchlorate exposure stemming from a U.S. National Academy of Sciences report were recently summarised[99,100] and call for ongoing investigations into safe thresholds for perchlorate exposure. Currently, there are no WHO guidelines for the regulation of perchlorate, although a meeting planned in 2010 by the United Nations and WHO plans for a full assessment of its toxicologic and exposure properties.[101]

Current recommendations

The most vulnerable populations of environmental perchlorate exposure are the developing foetus and newborn infant, as sufficient iodine nutrition is necessary for their normal thyroid function at a crucial time of neurodevelopment. Until more is known about the effects of environmental perchlorate exposure on iodine nutrition and thyroid function, adequate iodine nutrition in pregnant and lactating women should be optimised. Globally, the WHO has advised that in areas with uneven or lapsed iodised salt distribution (in which 20–90% of the households consume iodised salt), women of childbearing age should receive 150 μg

iodine per day.[104] The WHO recommends 250 μg of total iodine intake daily during pregnancy and lactation, and the U.S. Institute of Medicine recommends 220 μg during pregnancy and 290 μg during lactation.[102] Guidelines by the AmericanThyroid Association urge that prenatal vitamins for U.S. and Canadian women contain 150 μg iodine daily during pregnancy and lactation[103], and the U.S. National Academy of Sciences advocates that iodide be included in all prenatal multivitamins.[96]

In summary, improved detection methods in the past decade have allowed perchlorate to be measured in various food and water sources and across all populations in the U.S. Health implications of chronic, low-level, ubiquitous perchlorate exposure need to be further explored. The issue of environmental perchlorate exposure and its potential effects on thyroid function, particularly in the foetus and infant, remains controversial.

References

1. Godley AF, Stanbury JB. Preliminary experience in the treatment of hyperthyroidism with potassium perchlorate. The Journal of Clinical Endocrinology and Metabolism. 1954; 14:70–78. [PubMed: 13130654]
2. Crooks J, Wayne EJ. A comparison of potassium perchlorate, methylthiouracil, and carbimazole in the treatment of thyrotoxicosis. Lancet. 1960; 1:401–404. [PubMed: 13812986]
3. Bazailai D, Sheinfeld M. Fatal complication following use of potassium perchlorate in thyrotoxicosis. Israel Journal of Medical Sciences. 1966; 2:453–456. [PubMed: 4290684]
4. Wenzel KW, Lente JR. Similar effects of thionamide drugs and perchlorate on thyroid-stimulating immunoglobulins in Graves' disease: evidence against an immunosuppressive action of thionamide drugs. The Journal of Clinical Endocrinology and Metabolism. 1984; 58:62–69. [PubMed: 6196375]
5. Martino E, Aghini-Lombardi F, Mariotti S, et al. Treatment of amiodarone associated thyrotoxicosis by simultaneous administration of potassium perchlorate and methimazole. Journal of Endocrinological Investigation. 1986; 9:201–207. [PubMed: 3020113]
6. Reichert LJ, de Rooy HA. Treatment of amiodarone induced hyperthyroidism with potassium perchlorate and methimazole during amiodarone treatment. British Medical Journal. 1989; 298:1547–1548. [PubMed: 2547467]
7. Martino E, Mariotti S, Aghini-Lombardi F, et al. Short term administration of potassium perchlorate restores euthyroidism in amiodarone iodine-induced hypothyroidism. The Journal of Clinical Endocrinology and Metabolism. 1986; 63:1233–1236. [PubMed: 3020079]
8. Nolte W, Müller R, Siggelkow H, et al. Prophylactic application of thyrostatic drugs during excessive iodine exposure in euthyroid patients with thyroid autonomy: a randomized study. European Journal of Endocrinology. 1996; 134:337–341. [PubMed: 8616532]
9. Dasgupta PK, Dyke JV, Kirk AB, et al. Perchlorate in the United States. Analysis of relative source contributions to the food chain. Environmental Science & Technology. 2006; 40:6608–6614. [PubMed: 17144285]
10*. [23.04.09] International Council for the Control of Iodine Deficiency Disorders (ICCIDD). Available from: www.iccidd.org
11. [25.04.09] UNICEF World Summit for Children. Available from: http://www.unicef.org/wsc/declare.htm; 1990
12*. WHO, UNICEF, ICCIDD. A guide for programme managers. World Health Organization; Geneva: 2007. Assessment of the iodine deficiency disorders and monitoring their elimination.. WHO/NHD/01.1.
13. de Benoist B, Andersson M, Takkouche B, et al. Prevalence of iodine deficiency worldwide. Lancet. 2003; 362:1859–1860. [PubMed: 14654340]
14. Lazarus JH, Delange F. Prevalence of iodine deficiency worldwide. Lancet. 2004; 363:901. [PubMed: 15031052]

15*. Hollowell JG, Staehling NW, Hannon WH, et al. Iodine nutrition in the United States. Trend and public health implications: iodine excretion data from National Health and Nutrition Examination Survey I and III (1971-1974 and 1988-1994). The Journal of Clinical Endocrinology and Metabolism. 1998; 83:3401–3408. [PubMed: 9768638]

16*. Caldwell KL, Jones R, Hollowell JG. Urinary iodine concentration: United States National Health and Nutrition Examination Survey 2001-2002. Thyroid. 2005; 15:692–699. [PubMed: 16053386]

17. Dasgupta PK, Martinelango PK, Jackson WA, et al. The origin of naturally occurring perchlorate: the role of atmospheric processes. Environmental Science & Technology. 2005; 39:1569–1575. [PubMed: 15819211]

18. Furdui V, Tomassini F. Trends and sources of perchlorate in artic snow. Environ Sci Technol. 2010; 44:588–592. [PubMed: 19968271]

19. Snyder SA, vanderfod BJ, Rexing DJ. Trace analysis of bromate, chlorate, iodate, and perchlorate in natural and bottled waters. Environmental Science & Technology. 2005; 39:4586–4593. [PubMed: 16047796]

20. Srinivasan A, Viraraghavan T. Perchlorate: health effects and technologies for its removal from water resources. International Journal of Environmental Research and Public Health. 2009; 6:1418–1442. [PubMed: 19440526]

21. Stetson SJ, Wanty RB, Helsel DR, et al. Stability of low levels of perchlorate in drinking water and natural water samples. Analytica Chimica Acta. 2006; 567:108–113. [PubMed: 17723386]

22. Rao B, Anderson TA, Orris GJ, et al. Widespread natural perchlorate in unsaturated zones of the southwest United States. Environmental Science & Technology. 2007; 41:4522–4528. [PubMed: 17695891]

23. Urbansky ET, Brown SK, Magnuson ML, et al. Perchlorate levels in samples of sodium nitrate fertilizer derived from Chilean caliche. Environmental Pollution. 2001; 112:299–302. [PubMed: 11291435]

24. Barron L, Nesterenko PN, Paull B. Rapid on-line preconcentration and suppressed micro-bore ion chromatography of part per trillion levels of perchlorate in rainwater samples. Analytica Chimica Acta. 2006; 567:127–134. [PubMed: 17723389]

25. Krynitsky AJ, Niemann RA, Nortrup DA. Determination of perchlorate anion in foods by ion chromatography-tandem mass spectrometry. Analytical Chemistry. 2004; 76:5518–5522. [PubMed: 15362915]

26. Mathew J, Gandhi J, Hedrick J. Trace level perchlorate analysis by ion chromatography-mass spectrometry. Journal of Chromatography A. 2005; 1085:54–59. [PubMed: 16106848]

27. Yu L, Cañas JE, Cobb GP, et al. Uptake of perchlorate in terrestrial plants. Ecotoxicology and Enviornmental Safety. 2004; 58:44–49.

28. Blount BC, Ozpinar A, Alwis KU, et al. Perchlorate, nitrate, thiocyanate, and iodide levels in chicken feed, water, and eggs from three farms. Journal of Agricultural and Food Chemistry. 2008; 56:10709–10715. [PubMed: 18959414]

29. Renner R. Perchlorate found in vitamins and elsewhere. Environmental Science & Technology. 2006; 40:2498–2499. [PubMed: 16683580]

30. Environmental protection agency. Federal Register. 1998; 63:10274.

31. Dyke JV, Ito K, Obitsu T, et al. Perchlorate in dairy milk. Comparison of Japan versus the United States. Environmental Science & Technology. 2007; 41:88–92. [PubMed: 17265931]

32. El Aribi H, Le Blanc YJ, Antonsen S, et al. Analysis of perchlorate in foods and beverages by ion chromatography coupled with tandem mass spectrometry (IC-ESI-MS/MS). Analytica Chimica Acta. 2006; 567:39–47. [PubMed: 17723377]

33. Shi Y, Zhang P, Wang Y, et al. Perchlorate in sewage sludge, rice, bottled water and milk collected from different areas in China. Environment International. 2007; 33:955–962. [PubMed: 17604836]

34. Kannan K, Praamsma ML, Oldi JF, et al. Occurrence of perchlorate in drinking water, groundwater, surface water and human saliva from India. Chemosphere. 2009 [ePub ahead of print; PMID: 19328521].

35. Dai G, Levy O, Carrasco N. Cloning and characterization of the thyroid iodide transporter. Nature. 1996; 379:458–460. [PubMed: 8559252]

36. Smanik PA, Liu Q, Furminger TL, et al. Cloning of the human sodium iodide symporter. Biochemical and Biophysical Research. 1996; 226:339–345.
37. Eskandari S, Loo DD, Dai G, et al. Thyroid Na+/I− symporter. Mechanism, stoichiometry, and specificity. The Journal of Biological Chemistry. 1997; 272:27230–27238. [PubMed: 9341168]
38. De La Vieja A, Dohán O, Carrasco N. Molecular analysis of the sodium/iodide symporter: impact on thyroid and extrathyroid pathophysiology. Physiological Reviews. 2000; 80:1083–1085. [PubMed: 10893432]
39. Nicola JP, Basquin C, Portulano C, et al. American Journal of Physiology. Cell Physiology. 2009; 296:C654–C662. [PubMed: 19052257]
40. Tonacchera M, Pinchera A, Dimida A, et al. Relative potencies and additivity of perchlorate, thiocyanate, nitrate, and iodide on the inhibition of radioactive iodide uptake by the human sodium iodide symporter. Thyroid. 2004; 14:1012–1019. [PubMed: 15650353]
41*. Dohán O, Portulano C, Basquin C, et al. The Na+/I symporter (NIS) mediates electroneutral active transport of the environmental pollutant perchlorate. Proceedings of the National Academy of Sciences of the United States of America. 2007; 104:20250–20255. [PubMed: 18077370]
42. Tran N, Valentin-Blasini L, Blount BC, et al. Thyroid-stimulating hormone increases active transport of perchlorate into thyroid cells. American Journal of Physiology Endocrinology and Metabolism. 2008; 294:E802–E806. [PubMed: 18303123]
43. Valentin-Blasini L, Mauldin JP, Maple D, et al. Analysis of perchlorate in human urine using ion chromatography and electrospray tandem mass spectrometry. Analytical Chemistry. 2005; 77:2475–2481. [PubMed: 15828783]
44. Otero-Santos SM, Delinsky AD, Valentin-Blasini L, et al. Analysis of perchlorate in dried blood spots using ion chromatography and tandem mass spectrometry. Analytical Chemistry. 2009 [ePub ahead of print; PMID: 19199567].
45. Dyke JV, Kirk AB, Martinelango PK, et al. Sample processing method for the determination of perchlorate in milk. Analytica Chimica Acta. 2006; 567:73–78. [PubMed: 17723381]
46. Lawrence JE, Lamm SH, Pino S, et al. The effect of short-term low-dose perchlorate on various aspects of thyroid function. Thyroid. 2000; 10:659–663. [PubMed: 11014310]
47. Lawrence J, Lamm S, Braverman LE. Low dose perchlorate (3 mg daily) and thyroid function. Thyroid. 2001; 11:295. [PubMed: 11327623]
48. Greer MA, Goodman G, Pleus RC, et al. Health effects assessment for environmental perchlorate contamination: the dose response for inhibition of thyroidal radioiodine uptake in humans. Environmental Health Perspectives. 2003; 110:927–937. [PubMed: 12204829]
49. Braverman LE, Pearce EN, He X, et al. Effects of six months of daily low-dose perchlorate exposure on thyroid function in healthy volunteers. The Journal of Clinical Endocrinology and Metabolism. 2006; 91:2721–2724. [PubMed: 16636123]
50. Gibbs JP, Ahmad R, Crump KS, et al. Evaluation of a population with occupational exposure to airborne ammonium perchlorate for possible acute or chronic effects on thyroid function. Journal of Occupational and Environmental Medicine. 1998; 40:1072–1082. [PubMed: 9871884]
51. Lamm SH, Braverman LE, Li FX, et al. Thyroid health status of ammonium perchlorate workers: a cross-sectional occupational health study. Journal of Occupational and Environmental Medicine. 1999; 41:248–260. [PubMed: 10224590]
52. Braverman LE, He X, Pino S, et al. The effect of perchlorate, thiocyanate, and nitrate on thyroid function in workers exposed to perchlorate long-term. The Journal of Clinical Endocrinology and Metabolism. 2005; 90:700–706. [PubMed: 15572417]
53*. Braverman LE. Clinical studies of exposure to perchlorate in the United States. Thyroid. 2007; 17:819–822. [PubMed: 17705696]
54. Braverman LE. Environmental perchlorate: perhaps much ado about nothing. Endocrine Practice. 2009; 15:50–52. [PubMed: 19211399]
55. Blount BC, Valentin-Blasini L, Osterloh JD, et al. Perchlorate exposure of the US population, 2001-2002. Journal of Exposure Science & Environmental Epidemiology. 2007; 17:400–407. [PubMed: 17051137]

56*. Blount BC, Pirkle JL, Osterloh JD, et al. Urinary perchlorate and thyroid hormone levels in adolescent and adult men and women living in the United States. Environmental Health Perspectives. 2006; 114:1865–1871. [PubMed: 17185277]

57. Lamm SH, Hollowell JG, Engel A, et al. Perchlorate, thiocyanate, and low iodine association not seen with low creatinine-adjusted urine iodine among women of child-bearing age. Thyroid. 2007; 17:S51.

58*. Pearce EN, Lazarus JH, Smythe PP, et al. Thyroid function is not affected by environmental perchlorate exposure in first trimester pregnant women. Thyroid. 2007; 17:S42.

59*. Charnley G. Perchlorate: overview of risks and regulation. Food and Chemical Toxicology. 2008; 46:2307–2315. [PubMed: 18440116]

60. Cao XY, Jiang XM, Dou ZH, et al. Timing of vulnerability of the brain to iodine deficiency in endemic cretinism. The New England Journal of Medicine. 1994; 331:1739–1744. [PubMed: 7984194]

61. de Escobar DM, Obregon MJ, del Rey FE. Maternal thyroid hormones early in pregnancy and fetal brain development. Best Practice & Research Clinical Endocrinology & Metabolism. 2004; 18:225–248. [PubMed: 15157838]

62. Zoeller RT, Rovet J. Timing of thyroid hormone action in the developing brain: clinical observations and experimental findings. Journal of Neuroendocrinology. 2003; 16:809–818. [PubMed: 15500540]

63. Haddow JE, Palomaki GE, Allan WC, et al. Maternal thyroid deficiency during pregnancy and subsequent neuro-psychological development of the child. The New England Journal of Medicine. 1999; 341:549–555. [PubMed: 10451459]

64. Pop VJ, Kuijpens JL, van Baar AL, et al. Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. Clinical Endocrinology. 1999; 50:149–155. [PubMed: 10396355]

65. Alexander EK, Marqusee E, Lawrence J, et al. Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. The New England Journal of Medicine. 2004; 351:241–249. [PubMed: 15254282]

66. Glinoer D. The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. Endocrine Reviews. 1997; 18:404–433. [PubMed: 9183570]

67. Fisher DA, Klein AH. Thyroid development and disorders of thyroid function in the newborn. The New England Journal of Medicine. 1981; 304:702–712. [PubMed: 6258072]

68. Blount BC, Valentin-Blasini L. Analysis of perchlorate, thiocyanate, nitrate and iodide in human amniotic fluid using ion chromatography and electrospray tandem mass spectrometry. Analytica Chimica Acta. 2006; 567:87–93. [PubMed: 17723383]

69. Téllez RT, Chacón PM, Abarca CR, et al. Long-term environmental exposure to perchlorate through drinking water and thyroid function during pregnancy and the neonatal period. Thyroid. 2005; 15:963–975. [PubMed: 16187904]

70. Gibbs JP, Van Landingham C. Urinary perchlorate excretion does not predict thyroid function among pregnant women. Thyroid. 2008; 18:807–808. [PubMed: 18631015]

71. Pearce, EN.; Spencer, CA.; Mestman, J., et al. Thyroid Function is Not Affected by Environmental Perchlorate Exposure in First Trimester Pregnant Women from California and Argentina [abstract].. Endocrine Society 90th Annual Meeting; USA. 2009;

72*. Pearce, EN.; Lazarus, JH.; Smythe, PP., et al. Thyroid Function is Not Affected by Environmental Perchlorate Exposure in First Trimester Pregnant Women [abstract].. Endocrine Society 91st Annual Meeting; USA. 2009;

73. Brechner RJ, Parkhurst GD, Humble WO, et al. Ammonium perchlorate contamination in Colorado River drinking water is associated with abnormal thyroid function in newborns in Arizona. Journal of Occupational and Environmental Medicine. 2000; 42:777–782. [PubMed: 10953814]

74. Lamm SH. Perchlorate exposure does not explain differences in neonatal thyroid function between Yuma and Flagstaff. Journal of Occupational and Environmental Medicine. 2003; 45:1131–1132. [PubMed: 14610392]

75. Crump C, Michaud P, Téllez R, et al. Does perchlorate in drinking water affect thyroid function in newborns or school-age children? Journal of Occupational and Environmental Medicine. 2000; 42:603–612. [PubMed: 10874653]
76. Li FX, Byrd DM, Deyhle GM, et al. Neonatal thyroid-stimulating hormone level and perchlorate in drinking water. Teratology. 2000; 62:429–431. [PubMed: 11091365]
77. Kelsh MA, Buffler PA, Daaboul JJ, et al. Primary congenital hypothyroidism, newborn thyroid function, and environmental perchlorate exposure among residents of a Southern California community. Journal of Occupational and Environmental Medicine. 2003; 45:1116–1127. [PubMed: 14534454]
78. Amitai Y, Winston G, Sack J, et al. Gestational exposure to high perchlorate concentrations in drinking water and neonatal thyroxine levels. Thyroid. 2007; 17:843–850. [PubMed: 17956158]
79. Tazebay UH, Wapnir IL, Levy O, et al. The mammary gland iodide transporter is expressed during lactation and in breast cancer. Natural Medicines. 2000; 6:871–878.
80. Semba RD, Delange F. Iodine in human milk: perspectives for infant health. Nutrition Reviews. 2001; 59:269–278. [PubMed: 11518182]
81. Dohán O, De la Vieja A, Paroder V, et al. The sodium/iodide symporter (NIS): characterization, regulation, and medical significance. Endocrine Reviews. 2003; 24:48–77. [PubMed: 12588808]
82. Murray CW, Egan SK, Kim H, et al. US Food and Drug Administration's Total Diet Study: dietary intake of perchlorate and iodine. Journal of Exposure Science & Environmental Epidemiology. 2008; 18:571–580. [PubMed: 18167505]
83. Kirk AB, Martinelango PK, Tian K, et al. Perchlorate and iodide in dairy and breast milk. Environmental Science & Technology. 2005; 39:9391–9397. [PubMed: 16475313]
84. Pearce EN, Leung AM, Blount BC, et al. Breast milk iodine and perchlorate concentrations in lactating Boston-area women. The Journal of Clinical Endocrinology and Metabolism. 2007; 92:1673–1677. [PubMed: 17311853]
85. Leung AM, Pearce EN, Hamilton T, et al. Colostrum iodine and perchlorate concentrations in Boston-area women: a cross-sectional study. Clinical Endocrinology. 2009; 70:326–330. [PubMed: 18616704]
86. Kirk AB, Dyke JV, Marin CF, et al. Temporal patterns in perchlorate, thiocyanate, and iodide excretion in human milk. Environmental Health Perspectives. 2007; 115:182–186. [PubMed: 17384762]
87. Dasgupta PK, Kirk AB, Dyke JV, et al. Intake of iodine and perchlorate and excretion in human milk. Environmental Science & Technology. 2008; 42:8115–8121. [PubMed: 19031911]
88. Ginsberg GL, Hattis DB, Zoeller RT, et al. Evaluaton of the U.S. EPA/OSWER preliminary remediation goal for perchlorate in groundwater: focus on exposure to nursing infants. Environmental Health Perspectives. 2007; 115:361–369. [PubMed: 17431484]
89. Pearce EN, Pino S, He X, et al. Sources of dietary iodine: bread, cows' milk, and infant formula in the Boston area. The Journal of Clinical Endocrinology and Metabolism. 2004; 89:3421–3424. [PubMed: 15240625]
90. Schier JG, Wolkin AF, Valentin-Blasini L, et al. Perchlorate exposure from infant formula and comparisons with the perchlorate reference dose. Journal of Exposure Science & Environmental Epidemiology. 2009 [ePub ahead of print; PMID: 19293845].
91. Pearce EN, Braverman LE. Environmental pollutants and the thyroid. Best Practice & Research. Clinical Endocrinology & Metabolism. in press.
92. Howdeshell KL. A model of the development of the brain as a construct of the thyroid system. Environmental Health Perspectives. 2002; 110(Suppl. 3):337–348. [PubMed: 12060827]
93. Brucker-Davis F. Effects of environmental synthesis chemicals on thyroid function. Thyroid. 1998; 8:827–856. [PubMed: 9777756]
94. Boas M, Feldt-Rasmussen U, Skakkebaek NE, et al. Environmental chemicals and thyroid function. European Journal of Endocrinology. 2006; 154:599–611. [PubMed: 16645005]
95. Zoeller RT. Environmental chemicals impacting the thyroid: targets and consequences. Thyroid. 2007; 17:811–817. [PubMed: 17956155]
96. NRC (National Research Council). Health implications of perchlorate ingestion. National Academics Press; Washington DC: 2005.

97. U.S. Environmental Protection Agency. [21.04.09] Reference Dose (RfD): description and use in health risk assessments. Available from: http://www.epa.gov/NCEA/iris/rfd.htm

98. Crawford-Brown D, Raucher B, Harrod M. Intersubject variability of risk from perchlorate in community water supplies. Environmental Health Perspectives. 2006; 114:975–979. [PubMed: 16835046]

99. De Groef Decallonne BR, Vad der Geyten S, Darras VM, et al. Perchlorate versus other environmental sodium/iodide symporters: potential thyroid-related health effects. European Journal of Endocrinology. 2006; 155:17–25. [PubMed: 16793945]

100. Hershman JM. Perchlorate and thyroid function: what are the environmental issues? Thyroid. 2005; 15:427–431. [PubMed: 15929663]

101. Food and Agricultural Organization of the United Nations and World Health Organization. [25.04.09] Joint FAO/WHO Expert Committee on Food Additives. Available from: http://www.who.int/ipcs/food/jecfa/jecfa72.pdf

102. Food and Nutrition Board. Institute of medicine. Dietary reference intakes. National Academy Press; Washington, DC: 2006. p. 320-7.

103. Becker DV, Braverman LE, Delange F, et al. Iodine supplementation for pregnancy and lactation-United States and Canada: recommendations of the American Thyroid Association. Thyroid. 2006; 16:949–951. [PubMed: 17042677]

104. WHO Secretariat. Andersson M, de Benoist B, Delange F, Zupan J. Prevention and control of iodine deficiency in pregnant and lactating women and in children less than 2-years-old: conclusions and recommendations of the Technical Consultation. Public Health Nutrition. 2007; 10(12A):1606–1611. [PubMed: 18053287]

Research agenda

- The toxicological impacts of chronic, low-level environmental perchlorate exposure in combination with thyroid function monitoring should be studied.
- Perchlorate exposure and its inhibition of thyroidal iodine uptake should be assessed concurrently with other substances (e.g., thiocyanates in cigarette smoke and nitrates) that also affect iodine status by inhibiting the sodium iodide symporter.
- As foetuses and infants represent particularly vulnerable populations, additional research examining the relationships between iodine nutrition, perchlorate levels and thyroid function during pregnancy and in the post-partum period is warranted.
- The amount of maternal iodine intake needed to overcome the effects of perchlorate levels inhibiting iodine uptake in the foetus should be investigated.