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Environmental Perchlorate Exposure: Potential Adverse Thyroid Effects

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Abstract

Purpose of review—This review will present a general overview of the sources, human studies, and proposed regulatory action regarding environmental perchlorate exposure.

Recent findings—Some recent studies have reported significant associations between urinary perchlorate concentrations, thyroid dysfunction, and decreased infant IQ in groups who would be particularly susceptible to perchlorate effects. An update regarding the recent proposed regulatory actions and potential costs surrounding amelioration of perchlorate contamination is provided.

Summary—The potential adverse thyroidal effects of environmental perchlorate exposure remain controversial, and further research is needed to further define its relationship to human health among pregnant and lactating women and their infants.

Keywords

Perchlorate; thyroid; iodine; environment; regulation

Introduction

Perchlorate, an environmental contaminant, has been of concern in recent decades regarding its potential adverse effects on thyroid function. Environmental perchlorate exposure may result from the production of solid rocket fuel and other agents, through its incorporation into food and water supplies from groundwater accumulation, and from other sources. Some, but not all, studies have shown an association between urinary perchlorate concentrations (as a biomarker of environmental perchlorate exposure) and thyroid dysfunction. Though it remains controversial, U.S. legislation has been proposed to regulate perchlorate content of drinking water.

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Conflict of interest

None

Sources of environmental perchlorate exposure

Perchlorate is an inorganic anion present in low levels in the environment as a byproduct of solid rocket fuel and airbag manufacture (1), in fireworks displays (2), some crop fertilizers used in the U.S, and from its formation following natural atmospheric processes(3). Perchlorate acts as a potent competitive inhibitor of the sodium-iodide symporter (NIS) present on the basolateral membrane of thyroid follicular (4) and lactating breast (5) cells. In pharmacological doses, perchlorate decreases the active transport of iodine into the thyroid (6) and has the potential to result in thyroidal iodine deficiency, and in sufficiently high levels, may inhibit thyroid hormone synthesis. These effects may be additive, as one recent study shows that the thyroid gene expression profiles of perchlorate exposure and iodine deficiency are different, with the former demonstrating the accumulation of extracellular matrix proteins and the latter producing alterations in retinol and calcium signaling pathways (7). Historically, perchlorate was used pharmacologically to treat hyperthyroidism; although it is no longer medically available in the U.S., limited medical use of it continues in Europe and other regions (3).

Environmental perchlorate exposure is ubiquitous due to its high solubility and stability in groundwater(1), which represents a likely source of its incorporation into the U.S. food chain over the past few decades (8). Perchlorate has been detected in multiple crops, as well as in infant formula (9), cow's milk (10), and vitamins (11). From a study in the lower Colorado River region in California, perchlorate levels reached up to 1,816 ppb in locally-grown produce (12). One recent U.S. study reported that in a small cohort of lactating women, perchlorate intake through the diet may be an important source of exposure, compared to the women's consumption of local water (13). An analysis of National Health and Nutrition Examination Survey (NHANES) 2001-2008 subjects suggests that ingestion of certain foods groups, including milk, vegetables, fruits, and eggs, may be a source of perchlorate exposure in the U.S. diet, based on self-reported food consumption data (14). In the NHANES 2001-2002 cohort, perchlorate was detectable in low levels in the urine of all 2,820 U.S. adults sampled (median 3.6 µg/L) (15). Urine perchlorate levels have been commonly used as a biomarker of perchlorate exposure, and a recent study confirmed that a single spot urine measuring perchlorate concentration is reliable and representative of temporal exposure (16).

Perchlorate has also been detected in a variety of food sources in Canada, China, and India (3). A food and water market basket study in Japan from 2008-2009 reported that water ingestion contributed 0.5-22% of total perchlorate intake (17), while a sampling of 663 foods in Korea showed that perchlorate exposure from the diet there is less than the threshold levels recommended by the U.S. National Academy of Science (18). In another study, perchlorate was detectable in the serum of individuals residing in two Vietnamese cities; levels were higher among those in one industrial city containing factories for electrical and electronic waste recycling, compared to a control city (19).

Groups vulnerable to perchlorate exposure

Pregnant and lactating women and their developing infants are most susceptible to the effects of perchlorate exposure, given the crucial importance of adequate iodine and normal

thyroid function for proper neurodevelopment. Perchlorate has been detected in maternal serum, breastmilk, and colostrum of mothers and in cord blood, amniotic fluid, and infant urine (20,21). Among U.S. women of childbearing age, urinary perchlorate levels overall increased from 2005 to 2008 and were highest among Mexican-Americans and lowest in non-Hispanic Blacks (22). Breastfed infants had higher urinary perchlorate concentrations than formula-fed infants in one U.S. study (23).

Perchlorate is also actively transported by NIS in lactating breast cells (6) and can thus inhibit breastmilk iodine availability to the nursing infant. One study in New Jersey, U.S. reported a strong positive correlation between breastmilk perchlorate and urinary perchlorate levels among 106 women ($r=0.626$, $p<0.0005$) (24). However, these findings have not been consistent; although perchlorate was detectable in all breastmilk and urine samples in a study of 57 healthy lactating women in Boston, there was no association between breastmilk and urine perchlorate concentrations (25). Older infants and children are likely exposed to higher perchlorate levels when classified by body weight (26).

Human studies of environmental perchlorate exposure and thyroid function

The relationship between urinary perchlorate concentrations, a biomarker for environmental perchlorate exposure, and serum thyroid function remains extremely controversial. Studies of perchlorate exposure in both healthy volunteers and in occupational workers of perchlorate production have been recently reviewed elsewhere (3).

Analyses of the NHANES 2001-2002 dataset showed that urinary perchlorate concentrations were negatively associated with serum thyroxine and free thyroxine concentrations and positively associated with serum thyrotropin in women (but not men), particularly in those with urinary iodine concentrations less than 100 $\mu\text{g/L}$ (27,28). In the NHANES 2001-2002 sample, urinary concentrations of perchlorate, thiocyanate and nitrate as a collective measure were only weakly inversely associated with serum total thyroxine levels among all samples, but not when stratified by gender or only among those with urinary iodine concentrations below the median (29). Conversely, when the substances were individually assessed, although urinary perchlorate was detectable in all 1,641 samples from NHANES 2001-2002 (3.87 $\mu\text{g/L}$, geometric mean; 3.71-4.03, 95% CI), it was not associated with serum thyroid function, whereas urinary thiocyanate and nitrate levels were inversely associated with serum total thyroxine levels (29). Other reports have described a significant inverse association between urinary perchlorate levels and serum total thyroxine using the NHANES 2007-2008 dataset (30,31) and an inverse association with free thyroxine and a positive association with serum thyroid stimulating hormone (TSH) in first-trimester Thai pregnant women (32).

However, published data have not consistently supported an inverse relationship between perchlorate exposure and serum thyroid function. Subanalyses of the NHANES 2001-2002 dataset showed no significant correlation between urinary perchlorate concentrations and thyroid function among men (27) or women of childbearing age (33). Similar results have been reported in studies of pregnant women in Wales, Italy (34); Argentina; U.S. [Los Angeles, California] (35); and Greece (36). An ecological study in Chile of three cities with different perchlorate concentrations in drinking water, due to their relative proximities to

salt peter-containing mines in this region, showed no differences in serum thyroid function among pregnant women (who had a mean urinary perchlorate concentration of 114 µg/L in the city with the highest exposure) living in these regions when examined longitudinally (37). Similarly, in a study of a residential Sacramento, California [U.S.] region near a hazardous Superfund-designated site, there were no associations between urinary perchlorate concentrations, even when adjusted for urinary iodine concentrations, and serum thyroid function when studied 4-10 years following the capping of a perchlorate-contaminated drinking well (38). In one of the few reports examining the potential effect of perchlorate on infant health, there were no associations between perchlorate levels in breastmilk or maternal and infant urine with infant serum thyroid function (39). However, data from U.K. and Italian women and their infants in the Controlled Antenatal Thyroid Screening Study (CATS) demonstrated increased odds of infant IQ scores in the lowest 10% (assessed at age 3 years) when mothers' urinary perchlorate concentrations were in the upper 10% during pregnancy (40), despite the fact that maternal thyroid function was not significantly associated with perchlorate exposure (41). Furthermore, the lower infant IQ scores were not affected by levothyroxine therapy during pregnancy, suggesting the possibility that perchlorate may have had a direct effect on fetal thyroid function or on brain development.

Regulation of environmental perchlorate exposure

There is very limited regulation of perchlorate worldwide. Canada monitors perchlorate levels in drinking water and targets a recommended threshold of <6 µg/L, but this recommendation is not enforced (42).

The U.S. Environmental Protection Agency (EPA) has placed perchlorate on its Candidate Contamination List. In February 2011, the EPA proposed that action should proceed regarding national regulation of perchlorate in drinking water(43), including establishment of a national maximum contaminant level (MCL); this has been under review since May 2013 (44). In the U.S., California and Massachusetts are the only states to have set their own respective MCLs at 6 µg/L and 2 µg/L, respectively.

A 2009 report by the American Water Works Association (AWWA) estimated that the national costs of perchlorate regulation, in order to comply with a 4 µg/L MCL, would range up to \$120 million/year using single pass ion exchange to control all contaminated sources and entry points (45). An updated AWWA report in 2013 estimated the potential costs of perchlorate regulation according to various contamination concentrations and targeted MCLs. Using the example of treating a perchlorate concentration in the 90th percentile of previously sampled sites and a 2 µg/L MCL, the associated costs would approximate \$2.2 billion over 20 years(44).

The present recommendations by the U.S. Food and Drug Administration state that individuals of any age need not alter their diet or eating habits in relation to potential perchlorate exposure(46), but do agree with the recommendations by the American Thyroid Association that women who are planning pregnancy or who are pregnant or lactating should ingest a 150 µg iodine supplement daily (47) to ensure adequate iodine nutrition and to overcome the potential adverse effects of low-level perchlorate exposure.

Conclusions

Environmental perchlorate exposure appears to be ubiquitous and has been detected in various foods, groundwater, and in urine samples as a biomarker of human exposure. As a competitive inhibitor of NIS in thyroid follicular and lactating breast cells, it has the potential to decrease iodine availability and result in hypothyroidism when present in sufficiently high concentrations. Available data thus far have been inconsistent in demonstrating a correlation between low-level perchlorate exposure and thyroid dysfunction, particularly among those most vulnerable to even mild thyroid dysfunction. Ongoing research is needed to help better understand the potentially adverse effects of human perchlorate exposure, especially in light of recent discussion to proceed with costly longterm perchlorate regulation in U.S. drinking water.

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Abbreviations

AWWA	American Water Works Association
EPA	Environmental Protection Agency
MCL	maximum contaminant level
NHANES	National Health and Nutrition Examination Survey
NIS	sodium-iodide symporter
ppb	parts per billion

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Key points (3-5)

- Environmental perchlorate is ubiquitous, and urinary perchlorate (as a biomarker for exposure) has been detectable in low levels in several population studies.
- The potential adverse effects of perchlorate on thyroidal health, particularly among pregnant and lactating women and in infants, are unconfirmed.
- Additional studies are needed to support proposed legislation to regulate perchlorate exposure in drinking water.