

Statement for the House of Representatives'

Committee on Energy and Commerce

Subcommittee on Environment and Hazardous Materials

Hearing on the Health and Environmental Effects of Perchlorate

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Personal Information

Education and Training

M.D., Washington University School of Medicine, 1957
Residency Training: Barnes Hospital, St. Louis, 1957-61, 1963-4
Postdoctoral training: Endocrinology Branch, National Cancer Institute,
Bethesda, MD, 1957-1963

Faculty Appointments

Instructor and Assistant Professor of Medicine, Washington University
School of Medicine, 1964-69
Associate Professor and Professor of Medicine, University of Pennsylvania
School of Medicine, 1969-79
Verne Caviness Professor of Investigative Medicine, University of North Carolina
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Clinical Professor of Medicine, Harvard Medical School, 1989-present

Other

Editor-in-Chief, *Journal of Clinical Endocrinology and Metabolism*, 1982-88
Deputy Editor, *New England Journal of Medicine*, 1989-2000
Editor, *Clinical Thyroidology*, 2001-present
Co-Editor, *The Thyroid: A Fundamental and Clinical Text*,
6th, 7th, 8th, and 9th editions
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Implications of Perchlorate Ingestion, 2003-05

Personal Statement: I wish to make it clear that I am writing and speaking only for myself, not the National Academy of Sciences Committee (which in any event was disbanded when its report was completed and presented to the public in 2005). Also, I have never had any financial or other relationship with any manufacturer of perchlorate or of any perchlorate-containing products.

I take full responsibility of the content of this statement, but wish to acknowledge the assistance of Ellen Mantus, Ph.D., National Academy of Sciences, for preparation of some of the illustrations.

The Thyroid Gland and Its Hormones

The Thyroid Gland

The thyroid gland is a butterfly-shaped structure located in the front of the neck lying along the trachea. It weighs approximately 1 to 1.5 grams at birth and 10 to 20 grams in adults. It contains millions of follicles, each of which consists of a single layer of cells surrounding a cavity (lumen) containing thyroglobulin (Tg), a protein found only in the thyroid gland (Figure 1). Thyroglobulin is the framework for production and the storage of the two thyroid hormones, thyroxine (T₄) and triiodothyronine (T₃).

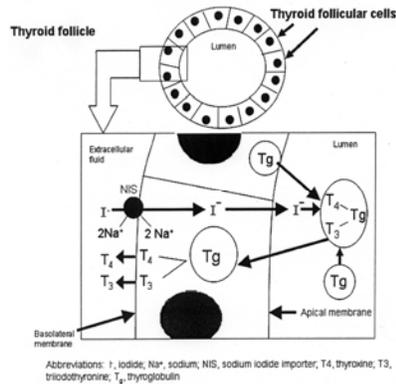


Figure 1. Diagram of a thyroid follicle and individual thyroid cell, showing the path of iodine and the formation of T₄ and T₃ with a thyroid cell and the adjacent lumen. From Health Implications of Perchlorate Ingestion. National Academy of Sciences. Washington, DC. 2005:37.

Thyroid Hormone

There are two thyroid hormones, thyroxine (T₄) and triiodothyronine (T₃) (Figure 2), and they are the only active substances that contain iodine (I).

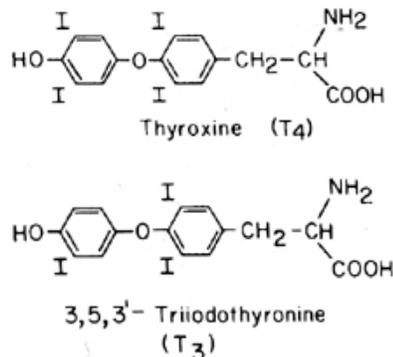


Figure 2. Structures of thyroxine (T₄) and triiodothyronine (T₃).

All of the thyroxine but only about 35% of the triiodothyronine produced each day comes from the thyroid gland. The remainder of the triiodothyronine is formed by removal of one iodine atom from thyroxine in most if not all tissues. Triiodothyronine is

the biologically active thyroid hormone, having in tissues approximately 100 times more activity than thyroxine. Nonetheless, thyroxine (T_4) is the term usually used, because it is the form of thyroid hormone that is most often measured and also given to people with hypothyroidism (thyroid deficiency).

Iodine and Thyroid Hormone

The iodine (as negatively charged iodide) needed to synthesize thyroxine and triiodothyronine must come from external sources (food and water). Once absorbed into the blood stream, it is transported into thyroid cells via a specific molecule known as the sodium/iodide symporter (NIS, Figure 1). (This symporter is also present in salivary glands, the stomach, and mammary glands, but iodide in these tissues is not further metabolized and returns to the blood stream.) Once inside thyroid cells, iodide rapidly traverses the cell and is transported into the lumen, where it is oxidized and combines with residues of tyrosine (an amino acid) within the thyroglobulin molecules to form the two hormones. The thyroglobulin is stored in the lumen or taken up by the cells and broken down to its constituent components, including thyroxine and triiodothyronine. The two hormones then are secreted into the blood stream.

Both thyroxine and triiodothyronine are largely bound to several proteins in the blood stream (>99%), and <1% is present as the free hormone. Therefore, there is a substantial reservoir of the two hormones in the circulation, should secretion from the thyroid temporarily decrease.

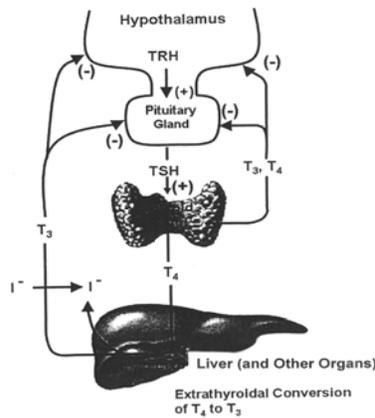
Entry and Action of Thyroid Hormone in Cells

Free thyroxine and free triiodothyronine in serum are carried into cells by transporter molecules in the cell membranes. Triiodothyronine is also available to cells because it is produced from thyroxine in them. Thus, there are two sources of triiodothyronine in cells, some enters the cells from the circulation and produced from thyroxine in the cells.

Many actions of thyroid hormone are stimulatory. It increases the production of several proteins in the heart, thereby increasing heart rate and contractility. In the liver, it increases the production of many different proteins required for growth, metabolism, and energy production. It also stimulates the production of proteins in the brain, most obviously during development. In contrast, in the pituitary gland, it inhibits the production of pituitary gland hormone known as thyroid-stimulating hormone (TSH, thyrotropin), a process termed negative feedback, which ultimately leads to a decrease in hormone synthesis by the thyroid gland.

Regulation of Thyroid Hormone Production

Thyroid hormone production is regulated primarily by the action of TSH (Figure 3). Pituitary secretion of TSH is inhibited by thyroxine and triiodothyronine and stimulated by a decrease in the two hormones. TSH secretion is also stimulated by thyrotropin-releasing hormone, produced in the hypothalamus. The conversion of thyroxine to triiodothyronine in many non-thyroid tissues is regulation by nutritional and illness-related factors.



TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone (also thyrotropin); T₄, thyroxine; T₃, triiodothyronine; I⁻, iodide: (-), inhibitory (negative) action; and (+), stimulatory (positive) action.

Figure 3. Diagram of hypothalamic-pituitary-thyroid Axis. TRH, thyrotropin-releasing hormone T₃ with a thyroid cell and the adjacent lumen. From Health Implications of Perchlorate Ingestion. National Academy of Sciences. Washington, DC. 2005:44.

The first mechanism provides a very sensitive defense against increases and especially decreases in thyroid hormone production. The second mechanism provides for rapid changes in the availability of T₃ in different tissues, especially in response to illness or starvation.

Iodide Nutrition and Metabolism

Iodide is essential component of thyroxine and triiodothyronine (Figure 2). It can be obtained only by ingestion of foods or liquids that naturally contain it or of foods to which iodide was added during processing (iodization). Foods with a high iodide content include seafood and sea products (kelp and seaweed), dairy products, eggs, commercial bakery products, and vegetables. Sea salt contains iodide, and iodized salt is widely available (and mandated by law in many countries).

Dietary iodide is absorbed and distributed rapidly (as iodide) through the blood stream, which also contains iodide released from the thyroid gland during hormone secretion and from extrathyroidal deiodination of the hormones. Iodide leaves the circulation by transport into the thyroid or by excretion in the urine.

The World Health Organization (WHO) recommends a dietary intake of 150 µg/day for adults, 200 µg/day for pregnant women, 90-120 µg/day for children 2-11 years old, and 50 µg/day for infants less than 2 years old. The Food and Nutrition Council of the Institute of Medicine of the National Academies recommends a slightly higher intake, 220 µg/day, for pregnant women (IOM 2000).

At those intakes there are no manifestations of thyroid dysfunction.

Progressively lower intakes are associated with thyroid enlargement (goiter), biochemical evidence of thyroid hormone deficiency, and ultimately, in those with severe iodide deficiency, hypothyroidism. The WHO definitions of iodide deficiency are: intake from 50 to 99 $\mu\text{g}/\text{day}$, mild iodide deficiency; intake of 20 to 49 $\mu\text{g}/\text{day}$, moderate iodide deficiency; and intake $<20 \mu\text{g}/\text{day}$, severe iodide deficiency. (Iodide intake is not measured directly but is usually estimated as the amount of iodide in a liter of urine.)

In 2001-2001, iodide intake in the United States averaged about 150 $\mu\text{g}/\text{day}$, based on measurements of urinary iodide excretion in several thousand children and adults (median urinary iodide excretion, 145 $\mu\text{g}/\text{L}$) (Caldwell et al., 2005). This value was about 50% lower than the value in 1971-1974. The value was less than 50 $\mu\text{g}/\text{day}$ days in 12% of adults (15% of women of childbearing age and 7% of pregnant women). There were no differences in serum TSH and thyroxine concentrations between those with urinary iodide values less than 50 $\mu\text{g}/\text{L}$ and those with higher values; apparently, the iodide intake in the former group was not low enough to cause a fall in T_4 secretion.

The reasons for the decrease in iodide intake in the United States between 1971-1974 and 2001-2002 are not known, but they include lower salt intake (iodized salt contains iodide at approximately 70 $\mu\text{g}/\text{g}$), less use of iodide in the baking and dairy industries, and less addition of iodide to animal feed.

Iodide deficiency is more prevalent in many other countries, and in many others it has been largely prevented by iodization of salt. I know of no reports of perchlorate exposure in areas of iodide deficiency.

Alterations in Thyroid Hormone Production

Severe iodide deficiency is one of many conditions that can reduce thyroid hormone production (and is the most common worldwide). Others include iodide excess, various drugs, congenital abnormalities of development of the thyroid gland, congenital deficiencies of thyroid hormone synthesis, and diseases that damage the thyroid gland. The range of thyroid deficiency in these conditions varies greatly, from those that are almost undetectable and fully compensated by the mechanism described below to severe hypothyroidism. Among infants, hypothyroidism can result in severe abnormalities in neural and skeletal development; in adults, it can result in substantial disability.

When thyroid gland synthesis and secretion of thyroid hormone fall as a result of iodide deficiency or any cause, the serum concentrations of the hormones fall. That results in a rapid increase in TSH secretion. If the thyroid is severely damaged or has been removed surgically or if the dose of an offending drug is high, TSH has little effect. Serum thyroid hormone concentrations continue to fall, and although TSH secretion increases further, severe hypothyroidism occurs. When the problem is iodide deficiency or if thyroid damage or drug blockade is incomplete, the initial increase in serum TSH concentrations stimulates synthesis and secretion of the two thyroid hormones sufficiently to raise their serum concentrations to normal or near normal. The rise in turn lowers TSH secretion to, or almost to, its original level. The person has no or few manifestations of hypothyroidism, although the thyroid gland may enlarge. Indeed, thyroid enlargement may be the only evidence that thyroid hormone production was low and TSH secretion was high earlier.

In conclusion, there is a potent mechanism—increased TSH secretion by the pituitary gland—to compensate for thyroid hormone deficiency. This compensation is activated by very small decreases in thyroid hormone production, and it effectively restores thyroid hormone production to normal or near normal even when the initial insult is substantial, for example, a fall in iodide intake (see next section).

Iodide Deficiency and Other Perturbations

The effects of iodide deficiency, depending on its severity, provide an example of the compensatory mechanism. People with mild iodide deficiency have normal serum thyroid hormone and TSH concentrations, but about 5-10% have some thyroid enlargement. Those with moderate deficiency also have normal serum thyroid hormone and TSH concentrations, but about 20-30% have thyroid enlargement. People with severe iodide deficiency may have slightly low serum thyroid hormone concentrations and high serum TSH concentrations, and over 30% have thyroid enlargement; overt hypothyroidism occurs only if iodide intake is below about 5-10 $\mu\text{g}/\text{day}$. As iodide intake declines, thyroid uptake of iodide increases because of an increase in the number of transport (NIS) molecules. This change constitutes another compensatory response; it is facilitated by an increase in TSH secretion but probably occurs even in the absence of an increase. Also, there is a shift to production of triiodothyronine, which contains less iodide but has more activity than thyroxine. In summary, there is remarkable compensation for the effects of iodide deficiency so that even when iodide intake is low normal or near-normal thyroid hormone production and TSH production are maintained. However, severe deficiency in iodide intake (below 20 $\mu\text{g}/\text{day}$) in pregnant women may result in major neurodevelopmental deficits and goiter in their offspring, and similar iodide deficiency in infants and children may result in smaller but still important neurodevelopmental deficits.

Iodide excess and therapy with lithium provide additional examples of the compensatory mechanism. In doses of 1,000 $\mu\text{g}/\text{day}$ or more, iodide has an antithyroid action in healthy subjects. In 1-2 weeks, serum thyroid hormone concentrations fall by 10-15% and serum TSH concentrations increase by about 50%. Those changes subside if intake of excess iodide continues. A similar pattern of changes in serum thyroid hormone and TSH concentrations occur in people with many thyroid disorders, including autoimmune thyroiditis, in which the thyroid is damaged by immune mechanisms and surgical removal of one side of the thyroid gland. In summary, many substances and conditions lower thyroid hormone secretion and result in a rise in TSH secretion. If the thyroid gland is not seriously damaged, the serum concentrations may return to normal, or so near to normal that there are few if any consequences.

Thyroid Hormone Actions in Developing Fetuses and Newborn Infants

Triiodothyronine is required for normal development of the central nervous system. Its actions include stimulation of the development and growth of nerve cells and supporting cells, the formation of connections between neurons, the formation of the myelin sheaths of nerves, and the development of the compounds transmit signals from one nerve cell to another. The resulting abnormalities in neurologic and neuropsychologic development, although variable and determined at least in part by when the deficiency occurred, are permanent, indicating that the correct timing of the

expression of genes in the brain during development is critical. However, the linkage between the biochemical abnormalities in the brain and the developmental abnormalities is not clear. Thyroid hormone is also needed for normal skeletal development and growth.

Effects of Perturbations of Maternal, Fetal, and Child Thyroid Function on Fetal and Child Development

The manifestations of hypothyroidism in infants vary, according to whether the mother, the fetus, or both have hypothyroidism and how long it persists. The abnormalities are greatest when both mother and fetus are affected; this is most likely to occur in regions of severe iodide deficiency. The consequences of severe maternal and fetal hypothyroidism during fetal life and in newborn infants include microcephaly (small brain), mental retardation, deaf-mutism, and movement disorders. These abnormalities are not reversible. However, the abnormalities can be largely prevented by administration of iodide to the mothers early during their pregnancies. That finding underlies the importance of the availability of thyroid hormone from the mother before fetal thyroid secretion begins.

The infants of mothers who have mild iodide deficiency have larger thyroid glands and higher serum TSH concentrations at birth than do those of mothers whose iodide intake is higher. Otherwise, they appear to be neurologically and physically normal.

Newborn infants who have hypothyroidism may have other abnormalities, including lethargy, poor muscle tone, poor feeding, and constipation, if not at birth then thereafter. The changes are similar to those that occur in older children and adults with hypothyroidism, and, in contrast with the neurologic abnormalities, they are reversible with adequate treatment.

Fetal and Neonatal Hypothyroidism

Infants who have even severe congenital hypothyroidism usually appear normal at birth. Their serum thyroid hormone concentrations are low, not very low, indicating that some maternal thyroid hormone crossed the placenta. Their serum TSH concentrations are high and rise further soon after birth. Those infants can be identified as having hypothyroidism by measurements of TSH or thyroxine in blood collected a few days after birth; this screening has been in place in the United States for about 30 years. Infants identified by neonatal screening have normal neural development and growth if aggressive thyroxine treatment is started within the first 2 or 3 weeks after delivery.

After birth, not only maternal thyroid hormone but also other maternal factors that might have affected fetal thyroid secretion are cleared from the infant's blood stream. Whether those substances alter a newborn infant's thyroid function depends on the dose and rate of clearance of the substance and the infant's maturity. The efficacy of prompt treatment of newborn infants found to have hypothyroidism by screening makes it unlikely that any rapidly cleared substance that reached the fetus from the mother and reduced thyroid secretion in the fetus, but no longer reached the infant after birth could cause postnatal hypothyroidism of sufficient severity to cause developmental delay.

That conclusion is born out by the uncommon clinical situation described below.

Hyperthyroidism (an overactive thyroid gland) occurs in about one in 2,000 pregnant women. Some of these women require treatment with an antithyroid drug throughout their pregnancies. The antithyroid drugs cross the placenta in sufficient quantities to cause fetal hypothyroidism. After birth, no more drug reaches the infant, the hormonal changes disappear rapidly, and the infants develop normally. Many years ago, some pregnant women with hyperthyroidism were treated successfully with potassium perchlorate. Most of the infants were normal, but one had slight thyroid enlargement that disappeared soon after birth.

Perchlorate and the Thyroid Gland

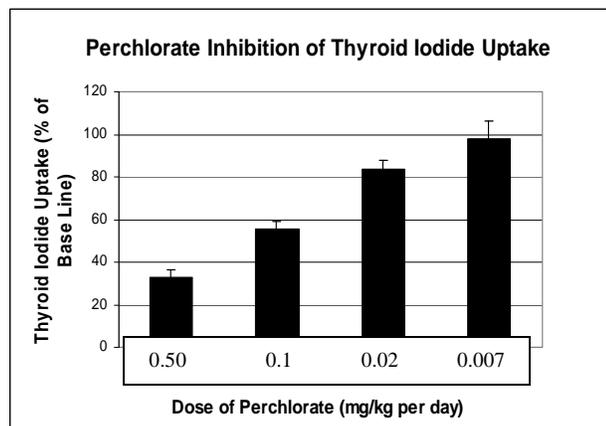
Perchlorate potentially can affect thyroid function because of its ability to block the transport of iodide into thyroid cells. As noted above, it competitively inhibits iodide transport into these cells. The fact that the inhibition is competitive means that it can be overcome by higher iodide concentrations of iodide, and, in laboratory studies, perchlorate did not inhibit uptake of iodide when high concentrations of iodide were present.

After recognition in the 1950s of the ability of perchlorate to block uptake of iodide in animal and then human thyroid tissue, it was given on a long-term basis in doses of 400 to 2000 mg (5.7 to 28.5 mg/kg body weight) daily to patients with hyperthyroidism, with the goal of reducing thyroid hormone synthesis and secretion. It proved to be safe, but its actions could be overridden by iodide, and about 10 years later it was replaced by newly developed antithyroid drugs.

Perchlorate Administration in Healthy Subjects

Potassium perchlorate has been given to a total of 72 healthy men and women for from 14 days to 6 months. The doses ranged from 0.007-9.2 mg/kg per day, assuming 70-kg body weight. The largest and longest of these studies are reviewed here.

Study 1. In a 14-day study, perchlorate was given in varying doses (0.5 to 0.007 mg/kg body weight) to 36 normal subjects (Greer et al. 2002). The lowest dose (0.007 mg/kg per day) did not statistically significantly inhibit thyroid uptake of radioactive iodide, but higher doses did inhibit uptake in a dose-dependent manner (Figure 4). There were no changes in serum thyroid hormone or TSH concentrations to suggest thyroid hormone production was adversely affected in this or any of the other studies.



Study 2. Administration of perchlorate (0.007 and 0.04 mg/kg body weight or placebo) to 13 normal subjects for 6 months (Braverman LE et al. 2006). There was no decrease in thyroid radioiodide uptake or change in serum thyroid hormone or TSH concentrations in the subjects given perchlorate (Table 1).

Clinical Study of Perchlorate

24-Hour Thyroid Iodide Uptake

	Baseline, 3 and 6 Months
Five subjects, 0.007 mg/kg per day	No decrease
Four subjects, 0.04 mg/kg per day	No decrease

Summary of Findings of These and the Three Other Available Clinical Studies

A dose of 0.007 mg/kg per day of perchlorate did not inhibit thyroid iodide uptake when given to healthy subjects for 2 weeks, 3 months, and 6 months. A dose of 0.04 mg/kg per day, which would inhibit thyroid iodine uptake by about 30% if given for two weeks, had no effect at 3 and 6 months (Lawrence JE et al. 2000; Lawrence JE et al. 2001; Brabant G et al. 1992).

There were no changes in serum thyroid hormone or TSH concentrations in any of the studies.

Model of Mode of Action of Perchlorate on the Thyroid Gland

Figure 5 shows what I believe is the correct model to assess and explain the action of perchlorate on the thyroid gland and the possible consequences of its action. This model also forms the basis for the conclusion that inhibition of thyroid iodine uptake is not an adverse effect.

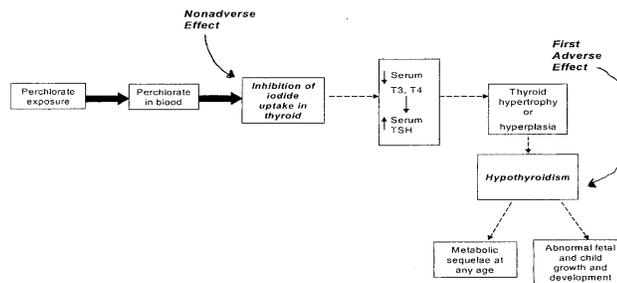


Figure 5. Mode-of-action model for perchlorate action showing the nonadverse effect of perchlorate used by the Perchlorate Committee in determining the reference dose of perchlorate.

From Health Implications of Perchlorate Ingestion. National Academy of Sciences. Washington, DC. 2005:167.

If there is no inhibition of thyroid iodine uptake, then there cannot not be any adverse effect. Furthermore, as noted before, there likely would be complete compensation within days for any mild to even moderate decrease in thyroid iodide uptake, as a result of increased TSH secretion, an increase in iodide transport into the thyroid gland, and increased conversion of thyroxine to triiodothyronine in many tissues.

This choice of no inhibition of thyroid iodine as a no-effect level led to the conclusion that 0.007 mg/kg body weight of perchlorate was safe, to which an uncertainty factor of 10 was added, yielding a reference dose to accommodate subjects, such as pregnant women, fetuses, and infants, perhaps more sensitive to the thyroid inhibitory action of perchlorate, resulting in a reference dose of 0.0007 mg/kg body weight. Furthermore, given the multiple compensation mechanisms, to cause declines in thyroid hormone production that would have adverse health effects, iodide uptake would most likely have to be reduced substantially for several months or longer.*

There are other data supporting this recommendation, such as studies of pregnant women, newborn infants, and children living in a town in Chile where the water contains 114 µg of perchlorate per liter and studies of newborn screening for hypothyroidism.

I continue to believe that the reference dose of 0.007 mg/kg body weight for perchlorate will protect all people for any harmful effects, and with a wide margin of safety.

Respectfully submitted.

Robert D. Utiger, M.D.

*One way to minimize the action of perchlorate on the thyroid is to increase iodide intake. Indeed, such an increase would benefit the entire U.S. population, given that iodide intake decreased by approximately 50% between 1971-1964 and 2001-2002, and conversely the proportions of people with mild or moderate iodide deficiency increased substantially. This could be done by increasing the iodide content of salt, making salt iodination mandatory, and adding iodide to all multiple vitamin products.

**New References Describing In Vivo Studies Published since The
Perchlorate Committee's Report Was Report Was Completed in 2005
(incomplete)**

Blount BC, et al. 2006. Urinary perchlorate and thyroid hormone levels in adolescent men and women living in the United States. Environ Health Perspect. 114:1865-1871.

Braverman LE, et al. 2006. Effects of six months of daily low-dose perchlorate exposure on thyroid function in healthy volunteers. J Clin Endocrinol Metab 91:2721-2724.

Tellez RT, et al. 2005. Long-term environmental exposure to perchlorate through drinking water and thyroid function during pregnancy and the neonatal period. Thyroid 15:963-975.

Multiple studies of measurements of perchlorate (and sometimes iodide) content of foods, beverages, and water have been published.

**References relevant to studies of thyroid physiology and disease and
the clinical studies of perchlorate may be found in the
Report of the Committee on Health Implications of Perchlorate Ingestion. 2005.
National Academy of Sciences. Washington, DC:68-74.**