

Clinical Studies of Exposure to Perchlorate in the United States

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Perchlorate is a competitive inhibitor of the sodium/iodine symporter, decreasing the active transport of iodine into the thyroid. It was used as an antithyroid drug in the treatment of hyperthyroidism in the 1950s and 1960s but was discontinued because of the occasional occurrence of aplastic anemia. More recently, lower doses of perchlorate have been used successfully in the treatment of iodine-induced hyperthyroidism. There has been concern that naturally occurring perchlorate and industrial contamination of water supplies with perchlorate might pose a health hazard by inducing or aggravating underlying thyroid dysfunction. In a series of studies in normal volunteers, administration of perchlorate from 2 weeks to 6 months and in perchlorate production workers exposed intermittently to high levels of perchlorate for years, no abnormalities of circulating thyroid hormones, thyroid-stimulating hormone, thyroglobulin, or ultrasound evaluation of thyroid structure were observed even though the thyroid ^{123}I uptake was decreased in some studies. Further studies of the effects of perchlorate on thyroid function in normal volunteers will now be difficult to carry out due to the adverse publicity that perchlorate and the studies on its effect have received.

PERCHLORATE IS A POTENT COMPETITIVE INHIBITOR of the sodium/iodine symporter (NIS), and when present in sufficiently high concentrations, it will decrease the active transport of iodine into the thyroid and decrease thyroid hormone synthesis. Thus, perchlorate was used in large doses in the 1950s and 1960s to treat hyperthyroidism (1). However, a few patients developed aplastic anemia during the administration of large doses of perchlorate (2), and thus it was not used for years in the therapy of hyperthyroidism. More recently, lower doses of perchlorate (up to 600 mg daily) have been used successfully and without serious side effects in the therapy of Graves' disease and iodine-induced hyperthyroidism (3,4).

Perchlorate salts are used as oxidizers in solid propellants for rockets and missiles, fireworks, road flares, matches, and airbag inflation systems. Perchlorate is also present in large concentrations in Chilean fertilizers used in the United States and in lower levels from natural processes (5). Perchlorate is extremely stable and poorly degraded. Following the development of high-performance liquid chromatography (HPLC) and, more recently, mass spectrometry to detect low levels of perchlorate, the anion has been detected in drinking water (ranging from 1 to 200 $\mu\text{g}/\text{L}$), a wide variety of foodstuffs including lettuce (6), and multivitamins (7). Contamination of ground water in regions of the United States where per-

chlorate was manufactured has raised concerns that low levels of perchlorate could pose a public health risk and cause thyroid disease.

The fetus and infant might be more susceptible to the adverse effects of perchlorate on thyroid function due to their smaller thyroid iodine pool and more rapid iodine turnover. However, several recent studies have not found any thyroid dysfunction in newborns, pregnant woman, and nonpregnant adults with normal iodine intake who were exposed to perchlorate in drinking water ranging from 4 to 340 μg perchlorate/L (8–10). One study that was conducted in two Arizona towns reported higher serum thyroid-stimulating hormone (TSH) concentrations in newborns whose mothers in one of the towns were exposed to 6 μg perchlorate/L in drinking water (11). The data were later reanalyzed with additional information and shown to be due to different demographics and altitudes between the two towns and not to perchlorate (12).

Since the lactating breast concentrates iodine through enhanced expression of NIS, Kirk *et al.* (13) reported that perchlorate was detected in cows' (median: 5.6 $\mu\text{g}/\text{L}$) and in human breast milk in concentrations up to 92 $\mu\text{g}/\text{L}$, which was associated with a decrease in breast milk iodine in the 6 of 36 individual samples with perchlorate concentrations greater than 10 $\mu\text{g}/\text{L}$. We have also reported that breast milk

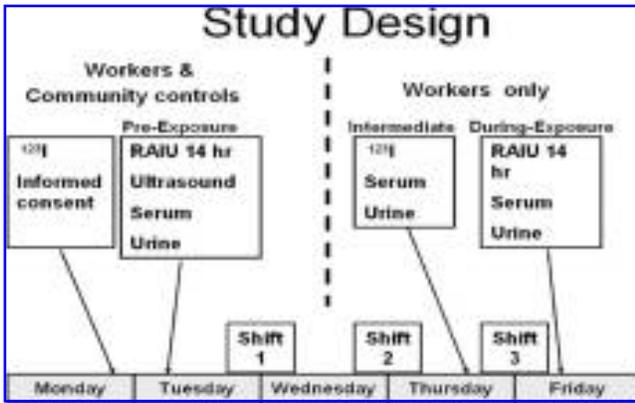


FIG. 1. The design of the study in the perchlorate production plant workers.

from lactating women in Boston contained perchlorate in all the samples from 49 women (median: $9.1 \mu\text{g}/\text{L}$; range: 1.3–411), and we did not observe any relationship between breast milk perchlorate and iodine concentrations, including the 23 women whose breast milk perchlorate values were $\geq 10 \mu\text{g}/\text{L}$ (14). There was, however, a significant decrease in breast milk iodine concentration in the women who smoked as assessed by urinary cotinine values, similar to that reported previously by Laurberg (15). It should be pointed out that perchlorate is also present in cows' milk in Japan (median: $9.3 \mu\text{g}/\text{L}$) (16) and in infant formulas in the United States (median: $1.5 \mu\text{g}/\text{L}$) (14).

We and others have carried out studies on perchlorate production workers exposed to excessive amounts of perchlorate and on normal volunteers given perchlorate from 2 weeks to 6 months to determine the effects of perchlorate on various aspects of thyroid function.

In the first two studies, normal volunteers with normal iodine intake were given 3 or 10 mg perchlorate daily in their drinking water for 14 days, and thyroid function tests, in-

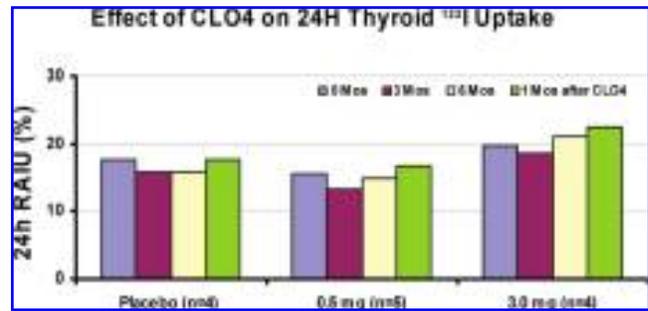


FIG. 3. The effect of 6 months of daily exposure to perchlorate in normal volunteers. There was no effect of perchlorate on any parameters of thyroid function.

cluding thyroid radioactive ^{123}I uptakes (RAIUs), were assessed before, during, and 14 days after perchlorate ingestion (17,18). No changes in serum thyroxine (T₄), free thyroid index (FTI), total triiodothyronine (TT₃), and TSH concentrations occurred at either dose of perchlorate even though significant serum and urine perchlorate levels were achieved. There was, however, a significant decrease in the thyroid RAIU on day 14 of perchlorate ingestion, and a small but significant increase above baseline 14 days after 10 mg perchlorate was discontinued. The 3 mg dose also had no effect on thyroid function including the thyroid RAIU, although a small increase above baseline in the RAIU occurred 2 weeks after perchlorate was discontinued, perhaps due to a small decrease in thyroid iodine content during perchlorate ingestion and/or upregulation of NIS. In another 14-day study in iodine-sufficient volunteers, Greer *et al.* (19) also found no effect of perchlorate on serum thyroid hormone and TSH concentrations in doses of perchlorate up to 35 mg daily, and reported a small decrease in the 24-hour RAIU on the 14th day at a daily dose of 1.4 mg perchlorate but no effect at 0.5 mg daily, suggesting that this dose is at the no-effect level. They did not observe a rebound increase in the RAIU after perchlorate was discontinued.

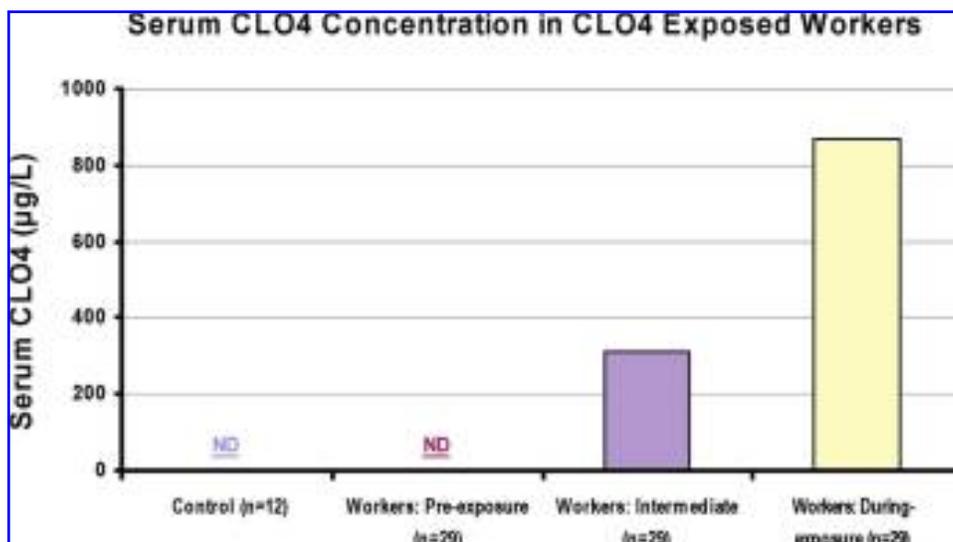


FIG. 2. The serum perchlorate concentrations in the perchlorate production plant workers. ND: not detected.

TABLE 1. CURRENT U.S. PERCHLORATE RECOMMENDATIONS

	No-effect level (RAIU)	Safety factor of 10	Water
National Academy of Sciences/ Environmental Protection Agency	7 $\mu\text{g}/\text{kg} \times 70 = 490 \mu\text{g}/\text{day}$	0.7 $\mu\text{g}/\text{kg} \times 70 = 49 \mu\text{g}/\text{day}$	24.5 $\mu\text{g}/\text{L}$
Massachusetts	7 $\mu\text{g}/\text{kg} \times 70 = 490 \mu\text{g}/\text{day}$		1 $\mu\text{g}/\text{L}$
California	7 $\mu\text{g}/\text{kg} \times 70 = 490 \mu\text{g}/\text{day}$		6 $\mu\text{g}/\text{L}$

RAIU: radioactive ^{123}I uptake.

Studies have been carried out in ammonium perchlorate production workers with normal iodine intake who were intermittently exposed to large concentrations of airborne perchlorate. Gibbs *et al.* (20) found no changes in thyroid function tests during long-term exposure, and Lamm *et al.* (21) also found no changes in serum TSH and circulating thyroid hormone levels in workers exposed to 0.5 mg perchlorate per kg per 12-hour shift. More recently, we have carried out further studies on perchlorate production workers and included thyroid ultrasounds and 14-hour thyroid RAIUs (22). These 29 workers had been employed in the plant for a minimum of 1.7 years and a median of 5.9 years. The study design is outlined in Figure 1. Mean spot urine perchlorate concentrations on the morning of the third successive night shift averaged 43 mg/g creatinine and were essentially undetectable after 3 days off work. Similarly, serum perchlorate concentrations were markedly elevated during perchlorate exposure (Fig. 2). There was a significant decrease in the 14-hour thyroid RAIU in the 29 workers during exposure (13.5%) compared to values in these workers after 3 days out of the plant (21.5%, $p < 0.01$). In spite of the decrease in the thyroid RAIU, there was no increase in serum TSH or thyroglobulin (Tg) values. However, during perchlorate exposure, there was a small but significant increase in urine iodine excretion, perhaps due to the decreased thyroid uptake of iodine, and a small but significant increase in serum T4, free thyroxine index (FT4I), and TT3 concentrations, perhaps due to an increased sensitivity of the mildly iodine-depleted thyroid to TSH. There was no difference in thyroid volume or pattern by ultrasound between the workers and 12 community controls not exposed to perchlorate. Finally, there were no differences in serum thiocyanate and nitrate concentrations, both weak inhibitors of NIS, between the workers and the community controls. Thus, these three studies have demonstrated that long-term, large but intermittent exposure to perchlorate does not adversely affect thyroid function in spite of a lowering of the thyroid RAIU.

A criticism of the above-discussed worker studies was that even though years of exposure to perchlorate essentially had no effect on thyroid function, the workers were not continually exposed to perchlorate. To obviate this problem, we carried out a blinded long-term 6-month study in 13 normal volunteers with normal iodine intake who were given daily capsules of placebo, 0.5 mg perchlorate, or 3 mg perchlorate (23). The study was underpowered due to the adverse publicity that perchlorate and the studies on its effect have received. However, no changes in the thyroid RAIU (Fig. 3) or in serum TSH, Tg, T4, FTI, and TT3 concentrations were observed in the placebo or the 0.5 mg and the 3 mg perchlorate groups in spite of concentrations of perchlorate in

the urine and serum, which were consistent with the doses of administered perchlorate.

Since this symposium and this manuscript were submitted for publication as part of the Proceedings, new information from the CDC has been published on the status of perchlorate in the United States. All urine samples from 2820 residents in the United States, as part of the National Health and Nutrition Examination Survey (2001–2002), contained perchlorate with a median value of 3.6 $\mu\text{g}/\text{L}$ (24). Further, serum TSH values in women whose urinary iodine values were $< 100 \mu\text{g}/\text{L}$ but not in women with urine iodine values $> 100 \mu\text{g}/\text{L}$ and not in men, regardless of their urine iodine values, were directly correlated with urine perchlorate (25). Serum T4 concentrations in these marginally iodine-deficient women were inversely related to their urine perchlorate values. It should be pointed out that these TSH and T4 changes were very small and that thyroid antibodies, a possible contributing factor in the women, were not measured. Further, we have very preliminary data in 396 pregnant women in Wales, an area of mild iodine deficiency, that urine perchlorate was detected in all their urines (median: 2.1 $\mu\text{g}/\text{L}$; mean: 6.4 ± 1.1 [SE] similar to the United States), and there was no correlation between urine perchlorate concentrations and serum TSH or FT4 values (unpublished, preliminary observations). Obviously, further studies are needed to clarify these findings.

It is evident that drinking water is not the only source of perchlorate in the United States. Nevertheless, the National Academy of Science has recently published its recommendation for perchlorate in drinking water (Table 1) (26). Further studies on the possible effects of perchlorate exposure on thyroid function would be helpful to help define any possible public health risk.

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