The Epidemiology of Environmental Perchlorate Exposure and Thyroid Function: A Comprehensive Review

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Objective: To review the epidemiological literature relevant to evaluating the risk of adverse effects on thyroid function associated with environmental perchlorate exposure. **Methods:** All studies investigating possible adverse effects of environmental perchlorate exposure on thyroid function in adults or in pregnant women and their newborns were critically evaluated. **Results:** There is no credible or consistent evidence from any of the numerous studies using a variety of designs that environmental exposure to perchlorate has any adverse effect on thyroid function, whether measured as changes in thyroid hormone levels or, among newborns, as the diagnosis of primary congenital hypothyroidism. The absence of adverse effects of environmental perchlorate on the thyroid likely reflects the very low perchlorate exposure levels worldwide, compared with much higher levels of exposure to nitrate and thiocyanate, goitrogens that inhibit thyroid function by the identical mechanism of action proposed for perchlorate. Adjusted for potency, perchlorate accounts for <1% of the inhibition of iodide uptake in the thyroid resulting from environmental exposure to nitrate and thiocyanate. Occupational studies of workers with substantially higher perchlorate exposure than the general population indicate that even extended exposure to high perchlorate levels does not adversely affect thyroid function. **Conclusion:** There is no epidemiologic evidence that environmental or occupational exposure to perchlorate adversely affects thyroid function in the United States. Even if all perchlorate could be removed from the environment, >99% of the inhibition of iodide uptake in the thyroid resulting from exposure to environmental goitrogens would remain.

Several comprehensive reviews have evaluated the evidence on potential adverse human health effects resulting from environmental exposure to perchlorate,[1–8] and their conclusions have been reassuring for the most part. A National Academy of Sciences (NAS) report recommended a perchlorate reference dose (RFD) of 0.7 μg/kg/d,[2] and subsequent reviews of the available epidemiological, clinical and laboratory evidence have concluded that there is no evidence of adverse health effects below this RFD.[3,5,6] Nevertheless, there remains considerable interest in establishing a very low permissible perchlorate level in drinking water, and some states have elected to set drinking water standards for perchlorate that are lower than the 15 μg/L limit proposed by the United States Environmental Protection Agency (USEPA) based on the recommended RFD.[5,8–10]

In this review, we critically examine the epidemiological literature relevant to the evaluation of potential toxic effects of environmental perchlorate exposure on thyroid function in the adult population overall and in the populations of pregnant women and their newborns who are speculated to be more susceptible to thyroid hormone disruption. In particular, we examine whether there is a reasonable, scientifically supported expectation of health risk reduction from placing lower allowable exposure limits on perchlorate, in view of the much higher levels of exposure of human populations to other goitrogenic chemicals, such as nitrate and thiocyanate.

The Sodium-Iodide Symporter, Thyroid Function, and Sodium-Iodide Symporter Inhibitors

Iodine is an essential element, obtained only through the diet, and is required for synthesis of thyroid hormones. Iodine is absorbed primarily by the gastrointestinal tract as the anion, iodide. The only known physiologic function of iodide is as a constituent of thyroid hormones. Iodide is transported into the thyroid gland by the sodium-iodide symporter (NIS), a first step leading to the subsequent organification of iodide and the formation of the thyroid hormones, triiodothyronine (T_3) and thyroxine (T_4).

Nitrate, thiocyanate, and perchlorate are anions that competitively inhibit NIS and, thus, can decrease the ability of NIS to transport iodide into the thyroid. Exposure to all three NIS inhibitors occurs through both natural and anthropogenic sources. Nitrate is ubiquitous in foods, both naturally occurring in green leafy vegetables and added as a preservative in processed meats.[11,12] Nitrate is also common in water sources, primarily because of the use of nitrate fertilizer in agriculture. Dietary sources of thiocyanate include numerous vegetables, such as cabbage, cauliflower, and broccoli, and milk and water.[12] Cigarette smoke is a major source of thiocyanate among smokers. Perchlorate occurs naturally worldwide at low levels[13] and has been detected at very low levels in the US food supply.[8,14] It has been detected in some US water sources, often as a result of industrial uses of perchlorate as a component of rocket fuel, munitions, and fireworks.[2,3,5,8]

The inhibitory mode of action of the three anions on the NIS has been shown to be through simple additive competition, with no evidence of synergy or antagonism.[2,3,12] According to a model for the physiological effects of NIS inhibition proposed in the NAS report,[2] gastrointestinal absorption of the NIS inhibitors leads to their presence in blood, which then decreases the uptake of iodide in the thyroid. At a sufficiently high level, NIS inhibition of iodide uptake leads to preclinical markers, namely, decreased plasma levels of T_3 and T_4, which in turn results in increased plasma levels of thyroid-stimulating hormone (TSH). TSH is produced in the anterior pituitary gland in response to low serum T_4 and T_3 levels, which then stimulates the thyroid gland to produce and secrete the thyroid hormones. The NIS is stimulated by TSH, leading to increased iodide uptake in the thyroid. As proposed by the NAS model, prolonged NIS inhibition at a high enough level will eventually lead to thyroid hypertrophy or hyperplasia and, subsequently, to hypothyroidism.[3] The effect of environmental NIS inhibitors has been likened to that of mild to moderate iodine insufficiency.[15]

Population Exposures to NIS Inhibitors

Relatively few studies have reported measurements of exposure levels to nitrate, thiocyanate, and perchlorate in the same human population. Exposures are typically reported in units of micrograms per liter for each anion in urine or blood samples. In

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evaluating the relative contribution of perchlorate to the overall iodide uptake inhibition (IUI) in the thyroid resulting from exposure to the three NIS inhibitors, it is necessary to take into account the relative IUI potencies of the three chemicals. However, the contribution of each of the three anions to overall NIS inhibition is a function not only of relative potency but also of exposure levels, and although perchlorate has the highest relative potency, human exposure levels to perchlorate are orders of magnitude lower than exposures to nitrate and thiocyanate.[3]

Perchlorate is a potent NIS inhibitor, and the relative potency of perchlorate to inhibit radioactive iodide uptake (RAIU) by NIS has been estimated to be 15 and 240 times that of thiocyanate and nitrate, respectively, on a molar concentration basis.[12] Estimates of the relative potencies have been remarkably consistent in both in vitro studies and in vivo rat studies,[3] and for measurements on a weight basis, the potency of perchlorate relative to thiocyanate and nitrate is 9 and 150, respectively.[12] Because thiocyanate has a longer half-life (~6 days) than perchlorate or nitrate (~5 hours or 8 hours, respectively), the physiologically relevant relative potencies of perchlorate and thiocyanate may actually be quite similar,[12] but the relative potency of 9 will be used in calculations below to maximize the estimated relative contribution of perchlorate to the overall IUI resulting from exposure to the three NIS inhibitors.

Studies of Population Exposure

A US study reported levels of the three NIS inhibitors in spot urine samples collected in the National Health and Nutrition Examination Survey (NHANES) during 2001 and 2002.[16] The geometric mean levels among girls aged 12 years or older were 38,000 μg/L for nitrate, 1200 μg/L for thiocyanate, and 2.84 μg/L for perchlorate. Taking the relative potencies into account, the relative contributions to NIS inhibition are estimated to be 65.0% for nitrate, 34.2% for thiocyanate, and 0.8% for perchlorate.

Another US study reported serum levels of the three NIS inhibitors among community controls for a study of workers occupationally exposed to perchlorate.[15] The mean serum levels were 7201 μg/L for nitrate and 3488 μg/L for thiocyanate. Perchlorate was not detected in control serum samples, but if the limit of detection at that time, 0.5 μg/L, is taken as the mean for perchlorate, then after adjustment for potency, the relative contributions to NIS inhibition are estimated to be 11.0% for nitrate, 88.9% for thiocyanate, and 0.1% for perchlorate.

An investigation in Israel reported serum levels of the three NIS inhibitors in populations with different perchlorate levels in their community drinking water sources.[17] Mean serum levels in women from the communities with high and low perchlorate water exposure were 4845 μg/L and 4661 μg/L for nitrate, 1906 μg/L and 1067 μg/L for thiocyanate, and 1.97 μg/L and 0.44 μg/L for perchlorate, respectively. The relative contributions to NIS inhibition are estimated to be 13.1% for nitrate, 86.1% for thiocyanate, and 0.8% for perchlorate in the high perchlorate exposure communities and 20.7% for nitrate, 79.0% for thiocyanate, and 0.3% for perchlorate in the low perchlorate exposure communities.

Tonacchera et al[12] reported that serum nitrate levels in the Western world are typically in the range 10 to 140 μmol/L, which correspond on a weight basis to the range of 620 to 11,450 μg/L. Similarly, they reported that serum thiocyanate levels in the Western world are typically in the range 10 to 70 μmol/L for nonsmokers (ie, 581 to 4066 μg/L) and 80 to 120 μmol/L for smokers (ie, 4647 to 6970 μg/L). Serum perchlorate levels have frequently been undetectable in previous studies, but the USEPA applied a physiologically based pharmacokinetic model[18] to the estimated 95th percentile perchlorate exposure level in the United States[19] to calculate a predicted 95th percentile for serum perchlorate level of 0.47 μg/L.[6] Using this estimated 95th percentile serum level for perchlorate and the lower limit of the ranges of typical nitrate and thiocyanate serum levels in Western populations, the percentage contribution of perchlorate to the overall NIS inhibition from exposure to the three anions is estimated to be 0.7% for nonsmokers and 0.1% for smokers.

In a recent investigation, researchers measured perchlorate, nitrate, and thiocyanate in amniotic fluid samples originally collected for amniocentesis in an Eastern US city.[20] Amniotic fluid samples provide measurements of chemicals known to have entered the fetal environment.[21] The median levels of nitrate, thiocyanate, and perchlorate were 1620 μg/L, 89 μg/L, and 0.18 μg/L, respectively. The corresponding percentage contributions to overall NIS inhibition in amniotic fluid for nitrate, thiocyanate, and perchlorate are estimated to be 51.8%, 47.4%, and 0.9%, respectively.

In summary, on the basis of the available information to date, it can be concluded that perchlorate is responsible for <1% of the IUI in the thyroid resulting from environmental exposure to nitrate, thiocyanate, and perchlorate in the United States and other Western populations. Although there have been reports of clinical or subclinical adverse effects on the thyroid resulting from environmental exposure to thiocyanate and to nitrate,[3,22–26] there have been no similar reports regarding environmental perchlorate exposure, likely reflecting low environmental perchlorate exposure levels worldwide.[13]

Multiple Regression Analyses of Urinary NIS Inhibitor Levels and Thyroid Hormone Levels

Multiple linear regression analyses have been conducted in recent cross-sectional studies to evaluate possible associations between urinary levels of nitrate, thiocyanate, and perchlorate and thyroid hormone levels in US populations.[16,27,28] Although the authors have claimed that these studies provide evidence of potential adverse effects from low level exposure to perchlorate, serious methodological weaknesses emanating from the study design, data, and statistical analyses preclude such conclusions of harm.

Two such studies were based on urine and blood samples collected as part of the NHANES during 2001 and 2002.[16,27] Nitrate, thiocyanate, perchlorate, and iodide were measured in spot urine samples, and TSH and total T_4 were measured in serum as possible preclinical markers of adverse thyroid effects. The authors of both the articles claim that significant correlations observed in multiple regression analyses with serum thyroid hormone levels as dependent variables and urinary chemical levels as independent variables provide evidence of possible adverse effects of perchlorate exposure at low levels. However, NHANES is a cross-sectional study, and therefore, no plausible causal inference is possible from the reported multivariate statistical analyses of data from such a study design. Cross-sectional studies collect information about outcomes (eg, thyroid hormone levels) and exposures (eg, perchlorate levels) at a single moment in time. Even if an outcome and an exposure appear to be associated, the temporal sequence is not ascertainable, and thus, it cannot be concluded with any degree of reliability that the exposure caused or even preceded the outcome. Although lower T_4 or higher TSH levels would obviously not cause higher perchlorate levels in the NHANES data, the methodologic limitations of a cross-sectional study design logically preclude the conclusion that higher perchlorate levels (detected in a single spot urine sample) caused lower T_4 or higher TSH levels in serum.

Both the studies based on the NHANES cross-sectional data are further weakened by the fact that the reported associations are observed only in select subgroups and are not supported by analyses of the entire NHANES study population.[16,27] The first study reported a positive association between perchlorate level and TSH level among women, and a negative association between perchlorate level and T_4 level among women with low iodine levels, where low iodine status was defined as having a urinary iodide level <100

μg/L.[16] Although it was reported that the negative association between perchlorate and T_4 was also observed among all women combined,[16] our independent multiple regression analysis of the same NHANES data, which replicated the subgroup analyses for women with low iodine and normal iodine reported in Tables 2 and 3, respectively, of the study,[16] found no significant correlation between perchlorate and T_4 level among all women ($P = 0.22$; data not shown). There was a nonsignificant positive correlation between perchlorate level and T_4 level among the two thirds of women with urinary iodide levels of 100 μg/L or greater,[16] which does not support the negative association observed for women with low iodine and is in the opposite direction of what would be expected on the basis of NIS inhibition caused by perchlorate.

Without presenting any results of regression analyses of data for men, the investigators reported that no association was observed between perchlorate level and either TSH or T_4 level among men, regardless of urinary iodide level.[16] The interpretation that the positive association between perchlorate and TSH levels in NHANES women is evidence of possible harmful effects caused by NIS inhibition is called into question by our independent analyses of the NHANES data for men, which showed marginally significant negative correlations between TSH level and both perchlorate level and thiocyanate level ($P = 0.07$ and $P = 0.03$, respectively; data not shown).

Further weakening the T_4 subgroup finding in this report[16] is the fact that the negative association between T_4 and perchlorate observed only in women with low iodine has been shown to be dependent on the units of measurement used to express iodide levels in the NHANES population.[29] Although 24-hour urine samples are preferable for measuring chemical exposures,[30] it has been demonstrated that creatinine-adjusted iodide levels provide a more reliable measure of iodine status than urinary iodide concentration per liter when based on spot urine samples.[29,31,32] In an independent analysis of the NHANES data, in which low iodine status was defined as having a urinary iodide level <100 μg of iodide per gram of creatinine, rather than <100 μg/L as in the original investigation, the association between perchlorate level and T_4 level in this subgroup of women with low iodine was neither negative nor statistically significant.[29]

In another analysis of the same NHANES data, it was reported that the negative association between perchlorate level and T_4 level was stronger among women with higher thiocyanate levels.[27] This synergistic interaction was observed only among women with low urinary iodine values, again defined as having a urinary iodide measurement <100 μg/L. There was no evidence for such an interaction in T_4 analyses among men; and despite the positive association reported in the original investigation between perchlorate level and TSH level among all women,[16] no evidence was found of an interaction between perchlorate and thiocyanate in analyses of TSH levels among women, regardless of iodine status.[27] The authors hypothesized that the absence of an interaction between perchlorate and thiocyanate in the TSH analyses might be explained by the fact that iodine deficiency is often characterized by decreased serum T_4 levels and normal serum TSH levels,[27] because of a TSH-independent autoregulatory mechanism, which leads to increased conversion of T_4 to T_3 and preferential synthesis of T_3 in the thyroid.[33] However, if such a TSH-independent regulatory mechanism is typical in response to NIS inhibitor exposure, then the significant positive association between perchlorate and TSH levels reported among NHANES women in both the investigations[16,27] cannot be invoked as evidence of an adverse effect of environmental perchlorate exposure on thyroid function.

It is important to note that one cannot empirically demonstrate an inhibitory effect of perchlorate on thyroid function in human populations separately from the effects of exposure to other NIS inhibitors, such as nitrate and thiocyanate.[2,3,6] This is true for all three of the major NIS inhibitors but is especially true for perchlorate, which makes such a small contribution to overall NIS inhibition compared with nitrate and thiocyanate. The claim that such an adverse effect of perchlorate can be conclusively demonstrated independent of the two major NIS inhibitors by means of multiple linear regression analyses in a nonexperimental study design is implausible.

Because thyroid hormones are regulated in a continuous dynamic process (homeostasis), there is general agreement that changes in serum thyroid hormone levels within the reference range, as reported in the multiple regression analyses of NHANES data for women,[16,27] cannot be interpreted as reflecting an adverse effect of exposure on thyroid function.[2,6] Thus, even if the correlations reported in these studies were based on a more informative and reliable study design and sound statistical analyses, they would be of doubtful relevance to assessing the potential for adverse pathologic effects of environmental perchlorate exposure on thyroid function. It has been argued that women with low iodine are a susceptible subgroup that may be more vulnerable to impaired iodide uptake resulting from perchlorate exposure.[16,27] There is, however, no evidence among US women of altered thyroid hormone levels associated with low iodine.[34,35] The US women with urinary iodide levels <50 μg/L (or <50 μg/g of creatinine) had normal levels of both TSH and T_4.[34,35] Normal thyroid hormone levels were also found among pregnant women, regardless of iodide level, when these women were evaluated separately.[35] Analyses of more recent NHANES data confirmed the adequacy of iodine nutrition in the US population, including among pregnant women.[36]

It has been hypothesized that pregnant women may also represent a population that is uniquely susceptible to potential adverse effects on thyroid function of NIS inhibition caused by perchlorate exposure. In a study of 184 pregnant women in 3 cities in northern Chile, multiple regression analyses were performed of urinary perchlorate concentrations and T_3, free T_4, TSH, and thyroglobulin levels.[37] Median urinary iodide level in this population was 269 μg/L, compared with the geometric mean level of 160 μg/L in pregnant women in the United States.[36] There was no significant association between urinary perchlorate excretion and any of the four thyroid function measures in this area with relatively high iodine intake.

Investigators are currently conducting a study to investigate the association between urinary perchlorate measurements and thyroid hormone measurements in several hundred pregnant women in Europe during their first trimester.[38] Urinary iodide levels in the European women are lower than those in US women and are considerably lower in some areas (eg, the median iodide level observed among 311 pregnant women from Turin, Italy, was 55 μg/L). Urinary perchlorate levels were comparable in the European women with those observed in the United States (eg, median perchlorate levels were 5.0 μg/L in Turin, 1.7 μg/L among 82 women in Dublin, Ireland, and 2.1 μg/L among 396 women in Cardiff, Wales, compared with the geometric mean for US women[16] of 2.8 μg/L). No association was observed in preliminary analyses among these pregnant women between urinary perchlorate levels and serum levels of either TSH or free T_4, even in analyses restricted to women with urinary iodide levels <100 μg/L.[38]

A recent report summarized a study in full-term infants between birth and 1 year of age of urinary measurements of nitrate, thiocyanate, perchlorate, and iodide, as well as urinary, rather than serum, measurements of TSH and T_4.[28] Urinary measurements of thyroid hormone levels have been found to be unreliable as indicators of hypothyroidism,[39,40] but even if urinary thyroid hormone levels are consistent with the more relevant serum thyroid hormone levels, the study results do not provide support for an adverse effect

of perchlorate exposure on thyroid function. The study reported that both urinary TSH and T_4 levels were positively associated with perchlorate level. These findings are inherently contradictory as evidence of the adverse effects of perchlorate via NIS inhibition. In the mechanistic model accepted by both the NAS and the USEPA,[2,6] NIS inhibition first leads to a decrease in serum T_4 levels, which then leads to increased TSH production by the pituitary gland, resulting in elevated serum TSH levels. Even the TSH-independent regulatory mechanism frequently observed as a result of mild to moderate iodine deficiency[33] would lead to decreased levels of serum T_4; so, the finding of higher T_4 levels in infants with higher perchlorate levels is not consistent with an adverse effect of perchlorate through any known mechanism.

Occupational Exposure to Perchlorate

Workers in ammonium perchlorate production plants have substantially higher perchlorate exposure than the general population. One investigation studied workers at a facility in Las Vegas, Nevada, who had been employed in the production of ammonium perchlorate for up to 27 years.[41] In evaluations of T_3, total T_4, free T_4, and TSH, no differences were observed between exposed and unexposed workers or between preshift and postshift measurements in exposed workers.[41] Standard clinical blood tests for liver, kidney, and bone marrow function also found no adverse effects of perchlorate exposure in this Las Vegas worker cohort.

In another study at an ammonium perchlorate plant in Cedar City, Utah,[42] no differences in levels of T_3, total T_4, free T_4, and TSH were found among four groups of workers defined by increasing perchlorate exposure levels, including a control group of azide production workers with only trace perchlorate exposure. The only comparison that approached statistical significance was a marginally significant increase in free T_4 observed with increasing perchlorate exposure, a finding in the opposite direction of what would be expected in the presence of perchlorate-induced NIS inhibition.[42]

An extensive subsequent investigation of thyroid function among workers at the Cedar City facility included detailed measurements for 29 exposed workers and 12 community control subjects, including ultrasound evaluation of the thyroid.[15] Serum levels of perchlorate, nitrate, and thiocyanate among the exposed workers were measured shortly after the completion of the third of three consecutive 12-hour night shifts and the morning before the first of three consecutive night shifts (ie, ~4 days after the end of the previous night shift). Serum levels of perchlorate were also measured just before the third of the three 12-hour night shifts (ie, ~12 hours after the end of the second shift). The mean serum levels at the completion of the three shifts were 838.4 μg/L for perchlorate, 7926.8 μg/L for nitrate, and 3487.8 μg/L for thiocyanate. The mean serum levels after 4 days off were 2.0 μg/L for perchlorate, 7638.6 μg/L for nitrate, and 3304.0 μg/L for thiocyanate. The mean serum perchlorate level 12 hours after completion of the second shift was 310.6 μg/L. As noted previously, no perchlorate was detected in the serum of the 12 community controls (the limit of detection was 0.5 μg/L), and the control mean serum levels were 7200.6 μg/L for nitrate and 3487.8 μg/L for thiocyanate. For the ammonium perchlorate workers, perchlorate would be predicted (after adjustment for potency) to be the major contributor to NIS inhibition for about half of the workweek. This is in marked contrast to the general population, for whom perchlorate contributes $<$1% of the total NIS inhibition resulting from environmental exposure to nitrate, thiocyanate, and perchlorate.

RAIU in the thyroid and serum thyroid hormone levels were determined the morning before the first shift and after completion of the third shift. No adverse effects from perchlorate exposure were observed among exposed workers in analyses of RAIU, T_3, total T_4, free T_4, TSH, or thyroglobulin.[15] Remarkably, mean serum levels of T_3, total T_4, and free T_4 were highest after the end of the third shift when serum perchlorate levels were highest. RAIU levels at the end of the third shift were similar to community control levels, whereas RAIU levels were significantly higher among perchlorate workers the morning before the first shift, compared with both the community controls and the workers' own RAIU levels after completion of the third shift. Ultrasound examinations revealed no differences in thyroid volume or pattern between the community controls and the exposed workers, who had a median 5.9 years (minimum 1.7 years) of employment in ammonium perchlorate manufacturing. Thus, this careful study of perchlorate manufacturing workers provided no evidence that extended exposure to high perchlorate levels adversely affects thyroid function. Because perchlorate was the major NIS inhibitor for much of each workweek among ammonium perchlorate workers, these results confirm that perchlorate is not unusually toxic to the thyroid compared with nitrate and thiocyanate.

Gestational Perchlorate Exposure and Newborn Thyroid Function

Numerous epidemiologic studies, primarily based on national or state newborn screening data, have evaluated the association between exposure of pregnant women to perchlorate in drinking water and various markers of thyroid function in their newborns, including TSH, T_4, and T_3 levels, and diagnoses by physicians of primary congenital hypothyroidism (PCH). Immediately after birth, there is a normal surge in TSH concentration and substantial hourly variability in TSH, which falls rapidly after the initial neonatal increase and stabilizes after the first 24 to 48 hours. Because of the extreme variation of TSH concentrations in the first day after birth, most epidemiologic studies of perchlorate exposure have excluded this time period altogether or restricted analyses to measures of thyroid function taken $>$24 hours after birth. Most newborns with elevated TSH levels in the first 24 hours after birth are normal (eg, 90% of California newborns in 1998[43] with TSH $>$25 μU/mL in the first 24 hours after birth were not diagnosed with PCH, compared with 40% of newborns with similarly elevated TSH $>$24 hours after birth). Accordingly, analyses of TSH in the first day after birth, even if tightly controlled statistically for hours since birth, would be of questionable validity for making inferences about adverse effects of perchlorate or any other potential goitrogen on thyroid function. Results of analyses of TSH values during the first 24 hours after birth cannot be interpreted as evidence of thyroid disease, and thus there is no biologic rationale or scientific justification for evaluating these very early TSH measurements in studies of potential harm from perchlorate exposure.

A study was conducted in Israel to examine neonatal T_4 levels after high gestational exposure to perchlorate in drinking water.[17] Perchlorate was detected in water up to a measured level of 340 μg/L, which far exceeds the drinking water equivalent level of 15 μg/L proposed by the USEPA.[9] Neonatal T_4 levels were obtained from a National Screening Program for congenital hypothyroidism, with samples taken 36 to 48 hours after birth for $>$90% of newborns, and were compared among newborns born during the first 9 months of 2004 in Morasha (n = 97; very high perchlorate exposure group, up to 340 μg/L), other neighborhoods of Ramat Hasharon (n = 216; high exposure group, 42 to 94 μg/L) and Hertzlia (n = 842; low exposure group, $<$3 μg/L). The areas were classified based on drinking water supply with respect to local wells and tap water samples taken during the study period. Mothers in the very high and high exposure groups were asked whether they drank tap water or other bottled water during pregnancy, and serum perchlorate levels (and thiocyanate, nitrate, and iodide levels) were measured in those participants who had been blood donors and used to validate the exposure differences among the three communities. Overall, neonatal T_4 levels were virtually identical in the three

groups of newborns (mean T_4 was 13.93, 13.91, and 13.98 μg/dL in very high, high, and low perchlorate exposure groups, respectively). In addition, no differences in T_4 levels were observed when those mothers in the very high ($n = 31$) and high ($n = 62$) exposure groups who drank only tap water, presumed to more closely reflect the perchlorate exposure of the drinking water source, when compared with the low exposure group. Serum perchlorate levels were significantly higher among donors residing in areas corresponding to very high or high exposure compared with low exposure, and the high perchlorate areas also had higher serum levels of nitrate and thiocyanate. Thus, the results of this study provide no evidence that environmental exposure to perchlorate or to the three NIS inhibitors combined has adverse effects on newborn thyroid function.[17]

The US investigators conducted a cross-sectional study within the California Newborn Screening Database in 1998,[43] by which time California had replaced a previously used two-tiered T_4-TSH screening program with a single-tiered TSH-only screening program (ie, all newborns were initially screened for elevated TSH levels). They examined the prevalence of PCH, as reported to the screening program by the newborn's physician, and elevated TSH (defined as >25 μU/mL) among 342,257 newborns residing in communities where groundwater had been tested for perchlorate. Newborns were dichotomized into perchlorate exposure groups of >5 μg/L ($n = 50,326$) and ≤5 μg/L ($n = 291,931$) based on the average perchlorate concentrations calculated for the mother's city of residence, with no individual quantitative estimates of exposure or water consumption patterns. Analyses of the disease endpoint of concern, PCH, provided no evidence of an association with perchlorate exposure; overall, 141 (0.05%) low-exposure newborns were diagnosed with PCH, compared with 15 (0.03%) high-exposure newborns, yielding a prevalence odds ratio (POR) of 0.71 (95% CI = 0.40 to 1.19) after adjusting for ethnicity, sex, birth weight, and multiple birth status.

With respect to TSH, 537 (0.18%) low-exposure newborns were identified as having high TSH, compared with 147 (0.29%) high-exposure newborns.[43] Although 36% of all newborns had their blood sampled for TSH screening at <24 hours of age, 80% of newborns with elevated TSH (>25 μU/mL) had their blood sampled for TSH screening during this period. Given the documented surge of TSH before 24 hours of age, followed by stabilization and further decline, the authors restricted the TSH analyses to newborns with age at specimen collection ≥24 hours (ie, 185,409 low exposure and 29,100 high exposure). Among these newborns, 14 (0.05%) with high exposure and 119 (0.06%) with low exposure had elevated TSH, yielding an adjusted POR of 0.73 (95% CI = 0.40 to 1.23) for the relationship between high perchlorate exposure and elevated TSH.

An earlier cross-sectional study within the California Newborn Screening Database (1983 to 1997) examined the prevalence of PCH and elevated TSH (defined dichotomously as assigned by the Screening Program, most commonly >25 μU/mL) among newborns of Redlands compared with San Bernardino and Riverside counties.[44] During the study period, California had a two-tiered T_4-TSH screening program, using a T_4 threshold of 9.0 μg/dL or the lowest 5% of remaining daily samples for subsequent measurement of TSH. Based on the California Department of Health Services Drinking Water Program, 15,348 newborns in Redlands (2081 of whom were TSH-screened) were considered exposed to perchlorate as a result of detection of perchlorate in groundwater wells (ranging from 4.0 to 130 μg/L), whereas 265,011 newborns (81,401 of whom were TSH-screened) in Riverside and San Bernardino counties (excluding communities where perchlorate had been detected) were considered unexposed, although again there were no individual quantitative estimates of exposure or water consumption patterns. As in the other study of California newborns,[43] the PCH analyses provided no evidence of an association with perchlorate exposure. Crude PCH prevalence rates were 28.5/100,000 births in San Bernardino/Riverside and 13.0/100,000 Redlands. There were two observed cases of PCH in Redlands during the study period, compared with 4.66 expected (adjusted for ethnicity, sex, birth weight, and birth year), yielding a standardized POR of 0.45 (95% CI = 0.06 to 1.64).

As expected, TSH levels had recovered from the neonatal surge and stabilized by ~20 hours after birth, with age at specimen collection as the strongest predictor of elevated TSH levels.[44] TSH analyses were adjusted for age (in hours) at time of specimen collection, with newborns older than 18 hours at time of specimen collection also examined separately. Overall, 44 newborns in Redlands had elevated TSH, 6 of whom were older than 18 hours at time of specimen collection. Compared with San Bernardino/Riverside, the odds ratio for elevated TSH in Redlands was 1.24 (95% CI = 0.89 to 1.68) among all newborns screened and 0.69 (95% CI = 0.27 to 1.45) among newborns with specimen collection age ≥18 hours.

In a longitudinal study in 2002 to 2004 of 184 pregnant women and 159 newborns in three cities in Northern Chile, TSH, free T_4, and T_3 levels were examined in the mother during gestation and in the newborn.[37] Perchlorate exposure was relatively well defined in this area. Mean perchlorate levels in the public drinking water were <0.5 μg/L in Antofagasta (no detectable perchlorate), 6 μg/L in Chanaral (low exposure), and 114 μg/L in Taltal (high exposure), in agreement with tap water samples taken from study participants and consistent with the observed distributions of urinary perchlorate excretion in the three cities. Median maternal urinary iodide level in all three cities combined was 269 μg/L, higher than levels reported in the United States,[16,36] but substantially lower than earlier levels reported in Chile. Mean perchlorate levels in 20 maternal prenatal serum samples and 14 cord serum samples from Taltal were 12.2 and 19.9 μg/L, respectively, substantially higher then the estimated 95th percentile serum perchlorate level in the US population of 0.47 μg/L.[6]

None of the thyroid hormone analyses in this population provided evidence of an adverse effect of perchlorate exposure on thyroid function.[37] After accounting for differences in maternal age, there were no significant differences between the three cities in free T_4 or TSH during either early pregnancy or late pregnancy. In fact, maternal TSH was lower in Taltal, the high perchlorate exposure city, than in Chanaral for early and late pregnancy and postpartum measures. A decrease in maternal free T_4 between the first and second prenatal visits was observed in all three cities. Significant differences observed at both prenatal visits among the three cities for T_3 levels were because of higher T_3 among women in Chanaral, the low exposure city, whereas Antofagasta (no exposure) and Taltal (high exposure) had similar T_3 levels. Among neonates, there were no significant differences in TSH or free T_4 levels among the three cities. In contrast to the maternal T_3 levels, neonates from Chanaral had significantly lower T_3 levels than neonates from the other two cities. The results of this study suggest that even drinking water perchlorate levels as high as 114 μg/L, as seen in Taltal, do not inhibit iodine uptake sufficiently to produce increases in TSH levels or decreases in T_3 or free T_4 either during gestation or among neonates.

An earlier study was conducted in the same three cities in Northern Chile to examine the following: 1) TSH levels and "presumed congenital hypothyroidism" (TSH ≥25 μU/mL) among 9784 newborns with National Program thyroid screening records between 1996 and 1999; and 2) TSH and T_4 levels among 162 school-age children who underwent thyroid examination, thyroid hormone analyses, and urinary iodine analyses (based on spot urine samples) in 1999.[45] Mean urinary iodide level among schoolchil-

dren was 720 μg/L, which is substantially higher than levels reported among children in the United States. The study provided no evidence that perchlorate in drinking water, at concentrations exceeding 100 μg/L, impairs thyroid function in newborns or schoolchildren. Among newborns included in this study, seven cases of presumed congenital hypothyroidism (TSH ≥25 μU/mL) were observed, all in Antofagasta, the city with no detectable perchlorate in drinking water. Median age at screening was 3 days in Antofagasta, compared with 4 days in Chanaral (low exposure) and 6 days in Taltal (high exposure); in each city, TSH levels peaked around day 3 and declined thereafter, whereas the TSH peak is generally observed much sooner after birth among newborns in the United States. Overall, average (and median) TSH levels were lower in Taltal than in either Antofagasta or Chanaral. Moreover, average and median TSH levels for newborns in Taltal were lower than or similar to those in Antofagasta and Chanaral for each day of screening, with the exception of days 1 to 2 after birth. In logistic regression analyses adjusted for sex and age at screening, average log TSH was significantly lower in Taltal compared with Antofagasta or Chanaral. Age at screening was a significant predictor of TSH, with significantly lower TSH levels at 4 days of life or greater compared with day 3. The observed TSH differences between the cities, whether clinically relevant or not, were in the opposite direction of what would be expected based on the hypothesized effects of perchlorate on newborn thyroid function and based on the known pharmacological effects of perchlorate in the thyroid.

Among the schoolchildren in this study, average TSH was nonsignificantly lower, and average free T_4 was significantly higher in Chanaral and Taltal compared with Antofagasta.[45] Again, these differences were in the opposite direction of what would be expected based on the hypothesized effects of perchlorate on thyroid function. Parents of schoolchildren in Taltal were significantly more likely to report a family history of thyroid disease compared with those in Antofagasta, although these self-reports were not validated and could reflect reporting bias.

In Arizona, a cross-sectional study was conducted of neonatal TSH levels among 1099 newborns in Yuma and 443 newborns in Flagstaff between October 1994 and December 1997.[46] Flagstaff is 250 miles from Yuma and 7000 ft higher in elevation. In Yuma, all drinking water is supplied by the Colorado River below Lake Mead (in which perchlorate has been detected), whereas in Flagstaff, none of the drinking water is supplied by the Colorado River below Lake Mead. No tap water samples or individual perchlorate exposures were measured, but drinking water measurements taken in 1999 showed perchlorate levels of 6 μg/L in Yuma and undetectable perchlorate in Flagstaff. In a two-tiered screening program, all newborns in Arizona are screened for T_4, and approximately 10% of the samples from each batch with the lowest T_4 levels are then screened for TSH. A higher percentage of T_4 values were sent for a TSH measurement in Yuma than in Flagstaff. Neonatal T_4 values did not differ between Yuma and Flagstaff after adjusting for race/ethnicity. In an analysis of variance adjusted for age in days at TSH measurement and race/ethnicity, the authors, without presenting summary estimates, report that the mean level of TSH for newborns in Yuma was significantly higher than in Flagstaff (P = 0.017). When data were stratified by age in days at TSH measurement and race/ethnicity, TSH levels seemed to be generally higher in Yuma than in Flagstaff, but none of the differences was statistically significant. Between 1994 and 1999, four cases of congenital hypothyroidism were reported in Yuma, compared with none in Flagstaff. The authors concluded that there is a significant association between perchlorate exposure and TSH concentrations in newborns.

The results of this Arizona study are at variance with virtually all other published results, and the methods have been criticized on several grounds, in particular the striking imbalance between Yuma and Flagstaff with respect to age at TSH sampling—almost 60% of newborns in Yuma had TSH measured on days 0 and 1, compared with only 30% in Flagstaff—and the noncomparability between the cities of Yuma and Flagstaff with respect to other regional factors such as elevation (known to be a strong determinant of iodine level and neonatal care, eg, supplemental oxygen use) and length of hospital stay. An independent scientifically sounder analysis of the Yuma City data using nearby comparison populations in Yuma County that had underground water sources reported no differences in TSH values between exposed Yuma City newborns and newborns from unexposed cities in Yuma County.[47]

In Nevada, investigators compared neonatal T_4 levels among 17,308 newborns in Las Vegas (perchlorate detected in water supplied from Lake Mead) with 5882 newborns in Reno (independent drinking water source with no detectable evidence of perchlorate contamination), from April 1998 through June 1999.[48] Lake Mead is the sole source of public water in Las Vegas, and perchlorate was detected (detection limit 4 μg/L) in Las Vegas drinking water for 7 of the 15 monthly measurements of perchlorate during the study period, ranging between 9 and 15 μg/L (time period A), and nondetectable during the other 8 months (time period B). The mean age at sample collection was significantly lower in Las Vegas (1.20 days) than in Reno (1.45 days) and was a significant predictor of T_4 levels. Birth weight was also significantly higher in Las Vegas than in Reno and was a significant predictor of T_4 levels. During the 15-month study period overall, and separately by time periods defined by months when perchlorate was or was not detected in Las Vegas water, mean neonatal T_4 levels did not differ between the two cities; mean T_4 levels over the entire study period were 17.11 μg/dL in Las Vegas and 17.12 μg/dL in Reno. Mean T_4 levels were lower during time period A than during time period B in both cities; thus, this period effect was not explained by the perchlorate exposure in Las Vegas.

In a related study, neonatal TSH levels were compared among 407 normal weight newborns in Las Vegas and 133 in Reno from December 1998 through October 1999.[49] The authors restricted the study to normal weight newborns because their data set demonstrated stable neonatal T_4 levels at a birth weight of 2500 g or greater, whereas below 2500 g, T_4 was strongly associated with birth weight. In Nevada, T_4 is the primary screening measurement for congenital hypothyroidism, and TSH is measured only among newborns in the lowest 10th percentile of T_4 measurements, which, thus, represent a subgroup with increased likelihood of congenital hypothyroidism. Measurements taken during the first day of life were excluded. Overall, mean TSH levels were 11.5 μU/mL in Las Vegas and 12.5 μU/mL in Reno, and levels did not differ significantly between the two cities, after adjustment for age during which the sample was taken and sex. TSH levels were significantly higher for samples taken during days 2 to 7 compared with those taken during days 8 to 30. When monthly TSH levels in each city were plotted against monthly perchlorate level in Las Vegas drinking water, there was no clear pattern of differences between the cities and no evidence of an association between TSH levels and perchlorate levels.

In an earlier investigation, researchers analyzed neonatal screening data for ~700,000 newborns in 1996 and 1997 to determine whether there was an increased incidence of congenital hypothyroidism in seven California and Nevada counties where perchlorate has been detected in drinking water sources.[50] Based on data provided by the respective state health departments, 249 cases of congenital hypothyroidism were observed in the seven counties in 1996 and 1997, compared with 243 expected, yielding a risk ratio of 1.0 (95% CI = 0.9 to 1.2). The risk ratio for each of the seven

counties separately ranged between 0.6 and 1.1. Expected numbers were adjusted for ethnicity. The results of this ecologic study are of limited value, because no information was provided by the authors on how congenital hypothyroidism was defined or whether it was similarly defined in each of the seven counties.

In summary, epidemiologic studies of pregnant women and their newborns have provided no evidence of impaired thyroid function, whether measured as increased rates of PCH, elevated TSH, or decreased T_4, resulting from environmental exposure to perchlorate levels in the United States or in other areas of the world having much higher perchlorate levels in water (eg, Taltal, Chile, or Ramat Hasharon, Israel). In fact, in many studies, observed effects were in the opposite direction of what would be expected based on the hypothesized toxic effects of perchlorate on newborn thyroid function and based on the known pharmacological action of perchlorate in the thyroid.

Experimental Studies in Humans and Therapeutic Use of Potassium Perchlorate

Analyses of observational epidemiologic studies are based on estimated perchlorate exposure levels. Information about potential adverse effects of perchlorate exposure is also available from experimental studies in which humans were administered known concentrations of potassium perchlorate and from a substantial literature on the therapeutic use of potassium perchlorate for the treatment or prevention of hyperthyroidism.[2,4,7] In the experimental studies, potassium perchlorate was administered to volunteers at known concentrations over periods ranging from 2 weeks to 6 months, and the effects of perchlorate exposure on thyroid function were determined. It was concluded by a NAS panel that there is no effect of perchlorate exposure on iodide uptake in the thyroid at doses below 7 μg/kg/d in healthy subjects.[2] Therapeutic use of potassium perchlorate to treat hyperthyroidism at high doses (up to 1000 mg/d) and for extended periods was helpful in restoring euthyroidism,[7] although such treatment, particularly with doses higher than 1000 mg/d, may have been associated with adverse hematologic events such as aplastic anemia or agranulocytosis.[51] Perchlorate therapy fell out of favor because of such adverse events, but perchlorate has subsequently been used safely in treatment of Graves' disease and iodine-induced hyperthyroidism.[7] Of particular interest is a report on the offspring of 12 women treated for hyperthyroidism at concentrations of 400,000 to 1,000,000 μg/d throughout their pregnancies.[52] Among the offspring of these 12 women, the only reported adverse event was a slightly enlarged thyroid gland in one infant, which resolved soon after birth. To put the NAS no effect level and the orders of magnitude higher therapeutic dose levels in perspective, the 95th percentile for environmental perchlorate exposure level for an US adult has been estimated to be 0.234 μg/kg/d,[19] which corresponds to a total dose of 16.4 μg/d in a 70-kg adult.

CONCLUSION

In summary, we have reviewed the epidemiologic studies investigating the potential for harmful effects of perchlorate exposure on thyroid function, including multiple regression analyses of urinary perchlorate levels and thyroid hormone levels in individuals with low level environmental perchlorate exposure; studies of thyroid hormone levels and thyroid RAIU in workers with prolonged occupational exposure to high levels of perchlorate; and investigations of the potentially more susceptible groups of pregnant women and newborns. The latter group of studies examined associations between maternal drinking water perchlorate exposure and thyroid hormone levels in women and their newborns, and between the maternal perchlorate levels and the clinically relevant endpoint in newborns, PCH. These various types of studies provide no consistent or credible evidence of an association between environmental perchlorate exposure and adverse thyroid function. In fact, it is notable that many of the reported associations were in the opposite direction of what would be expected if NIS inhibition from perchlorate exposure results in thyroid dysfunction in the general population or in the conjectured at-risk subgroups. Moreover, perchlorate exposure in the United States and other Western countries appears to account for $<1\%$ of the inhibition of iodide uptake in the thyroid resulting from environmental exposure to nitrate, thiocyanate, and perchlorate, so that even if all perchlorate could be removed from the environment, $>99\%$ of the impact of environmental exposure to NIS inhibitors on iodide uptake in the thyroid would remain. The absence of evidence from epidemiological studies using various study designs that environmental perchlorate exposure adversely affects thyroid function and the documented low levels of environmental perchlorate exposure in the United States lead to the conclusion that efforts to place a stringent allowable drinking water limit on perchlorate are not supported by the weight of the scientific evidence.

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