Gestational Exposure to High Perchlorate Concentrations in Drinking Water and Neonatal Thyroxine Levels

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Objective: To assess the effect of gestational perchlorate exposure through drinking water on neonatal thyroxine (T_4). *Design*: T_4 values were compared among newborns in Ramat Hasharon, Israel, whose mothers resided in suburbs where drinking water contained perchlorate $\leq 340\,\mu g/L$ (very high exposure, $n = 97$), 42–$94\,\mu g/L$ (high exposure, $n = 216$), and $<3\,\mu g/L$ (low exposure, $n = 843$). In the very high and high exposure areas, T_4 values in newborns whose mothers drank tap water exclusively (as determined by a telephone interview) were analyzed as a subset. Serum perchlorate levels in blood from donors residing in the area were used as proxy indicators of exposure. *Main outcome*: Neonatal T_4 values (mean ± SD) in the very high, high, and low exposure groups were 13.9 ± 3.8, 13.9 ± 3.4, and $14.0 \pm 3.5\,\mu g/dL$, respectively ($p = NS$). Serum perchlorate concentrations in blood from donors residing in areas corresponding to these groups were 5.99 ± 3.89, 1.19 ± 1.37, and $0.44 \pm 0.55\,\mu g/L$, respectively. T_4 levels of neonates with putative gestational exposure to perchlorate in drinking water were not statistically different from controls. *Conclusion*: This study finds no change in neonatal T_4 levels despite maternal consumption of drinking water that contains perchlorate at levels in excess of the Environmental Protection Agency (EPA) drinking water equivalent level ($24.5\,\mu g/L$) based on the National Research Council reference dose (RfD) [$0.7\,\mu g/(kg \cdot day)$]. Therefore the perchlorate RfD is likely to be protective of thyroid function in neonates of mothers with adequate iodide intake.

Introduction

PERCHLORATE CAN AFFECT THYROID FUNCTION by competitive inhibition of iodide uptake into the thyroid. Potassium perchlorate was used in the 1950s and 1960s for treatment of hyperthyroidism at doses of 400–2000 mg/day for many weeks or months. This use of perchlorate ceased by the late 1960s because it was found to cause aplastic anemia and agranulocytosis, including seven fatalities (1,2). Interest in perchlorate has resurged due to its widespread contamination of drinking water from military and other industrial uses. In Arizona, California, and Nevada alone, the drinking water supply for about 20 million people is contaminated to some degree by perchlorate (3). The range of proposed regulation of perchlorate in drinking water varied between $2\,\mu g/L$ (4) and $220\,\mu g/L$, as suggested by the Department of Defense (5). A too stringent drinking water standard for perchlorate would necessitate an expensive clean-up as 35 states have more than $4\,\mu g/L$ of perchlorate in drinking water. Drinking water standards are preferably based on risk assessment of the critical effect of a chemical in humans when data are available (6). To account for the intraspecies variability, studies should consider the most sensitive population—in the case of perchlorate, fetuses of pregnant women (2). The National Research Council (NRC) of the National Academy of Sciences recommended a reference dose (RfD) of $0.7\,\mu g/(kg \cdot day)$ based on a clinical study of 37 adult volunteers by Greer *et al.* (1). In this study, the no-observed-effect level (NOEL) for inhibition of iodide uptake by the thyroid was $7\,\mu g/(kg \cdot day)$ perchlorate. An additional uncertainty factor of 10 was introduced to protect the most sensitive population, that is, fetuses of pregnant women. A drinking water equivalent level (DWEL) of 24.5 $\mu g/L$ can be extrapolated from the RfD based on a 70-kg person drinking 2 L water/day, and no perchlorate exposure from other sources.

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Data on the effect of perchlorate exposure on thyroid function in susceptible populations would provide a stronger basis for risk assessment. Several epidemiological studies have assessed the association between exposure to perchlorate in pregnant women and thyroid function of their offspring (3,7–11). Perchlorate concentrations in drinking water were up to 115–120 μg/L in two studies from Chile (8,12), and <16 μg/L in five reports from the United States. All studies except that of Brechner *et al.* (3) showed no association between exposure to perchlorate in pregnant women and effect on thyroid functions in their newborns. The methodology of the Brechner study has been severely criticized (13,14). These U.S. studies, as well as the present study (see "Discussion"), were conducted in iodine-sufficient areas and did not include individual iodine status measures. These studies are insufficient because, with the exception of Tellez *et al.* (12), they were ecological studies, which did not ascertain actual exposure of the individual pregnant mother to perchlorate. The Tellez *et al.* (12) study from Chile reported direct measurements of perchlorate intake and showed that gestational exposure to perchlorate at 114 μg/L in drinking water did not cause changes in neonatal thyroid function or fetal growth retardation. This study had not been peer reviewed at the time of the NRC assessment. Direct evidence on the effect of gestational perchlorate exposure on thyroid functions of newborns in humans was judged inadequate; therefore, experimental data in adults were reviewed as a second best alternative. Since the critical effect of perchlorate is impaired thyroid function in human fetuses, data on the effect of high gestational exposure to perchlorate on the thyroid function of newborns would contribute to a more reliable basis for its regulation in drinking water.

Herein we tested the null hypothesis that there would be no significant differences in neonatal thyroxine (T$_4$) levels following high gestational exposure to perchlorate in drinking water, in iodine-sufficient pregnant women. Our study addressed perchlorate concentrations in drinking water that were substantially above the recommended DWEL of the EPA as derived from the RfD established by the NRC (2).

Materials and Methods

Population and water perchlorate data

Ramat Hasharon is a city located in central Israel close to the Mediterranean coast with 35,600 inhabitants in 2004. Perchlorate contamination of groundwater was found in local wells that had been in the vicinity of a military plant that was active for decades (Fig. 1). Until October 2004, drinking water was supplied to this city exclusively from local wells (mainly wells A–E), whereas well H mainly supplied the suburb Morasha with 15,000 inhabitants, located in close proximity to the military plant.

In August 2004, water samples (in duplicates) were sent for assessment of perchlorate levels to two laboratories in the United States, Knoxville, Tennessee, and Savannah, Georgia. The following results were reported: the well that supplied Morasha had a perchlorate concentration of 684 μg/L as reported by the laboratory in Savannah and 1100 μg/L as reported by the laboratory in Knoxville. The wells supplying the other neighborhoods in Ramat Hasharon had perchlorate water concentrations in the range 63–88 μg/L (Savannah laboratory) and 50–62 μg/L (Knoxville laboratory). Upon receiving these results, the Israeli Ministry of Health ordered an immediate closure of the well in Morasha, whereas the other wells remained active until July 2005. A second set of water samples was taken from these wells on October 4, 2004, and the perchlorate
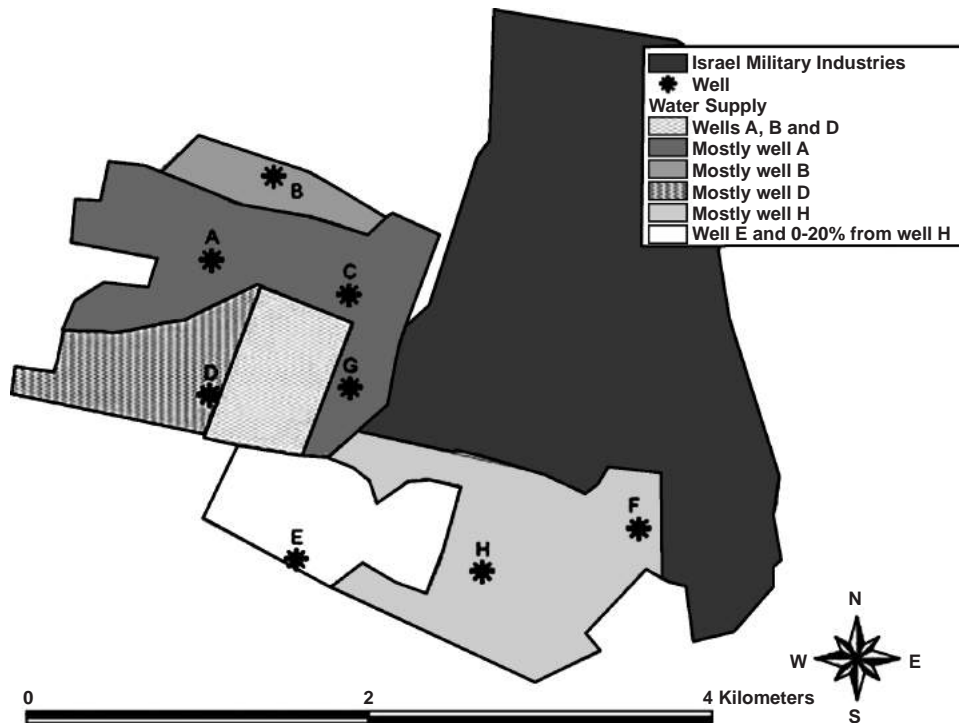

FIG. 1. Map showing well H, which was the primary drinking water source for Morasha (light gray area at the bottom). Wells A through E (remaining area in the figure) supplied the remaining area of Ramat Hasharon.

concentration in the well at Morasha remained 1100 μg/L. The wells supplying the other neighborhoods had perchlorate concentrations of 49–68 μg/L in October 2004, and 42–94 μg/L in March and April 2005. Four tap water samples taken from homes in these neighborhoods in April 2005 had similar concentrations of perchlorate (42–80 μg/L) as determined by the Savannah laboratory. By contrast, only one residential tap water sample in the highest exposure area was assayed for perchlorate before its closure on October 4, 2004, and the concentration was 340 μg/L.

The study population consisted of all singleton newborns born during the period January 1–September 30, 2004, whose mothers resided in Morasha (very high exposure group), the other neighborhoods of Ramat Hasharon (high exposure group). Only newborns who were born in hospitals and were screened by the Israeli National Newborn Screening (NBS) Program for congenital hypothyroidism (>99%) were considered. Newborns from a neighboring city, Hertzlia (with 83,500 inhabitants), with water perchlorate concentrations <2 μg/L in six samples and 2–2.7 μg/L in five samples, served as a control.

Newborn screening data

The Israeli NBS Program is a nationwide screening program for congenital hypothyroidism and phenylketonuria administered by the Ministry of Health. All newborns undergo blood sampling drawn by heel stick for T_4 and phenylalanine predischarge, at the age of 36–48 hours for >90% of newborns. In premature infants, the sampling is done at the age of 1 week. The same routine is held in all hospitals in Israel. All T_4 blood levels were assayed as previously described (15–17) at the central laboratory of the Sheba Medical Center, Tel Hashomer.

Initial exposure assessment

Figure 1 shows the water supply of Ramat Hasharon with respect to the local wells. A computerized, geo-referenced file of this information was then created (shape-file). All births in Ramat Hasharon during the study period were geo-coded according to maternal residential address. Those infants not geo-coded were located manually. This file of geo-referenced births was then linked to the hospital T_4 data using identity number as a unique identifier. Thus T_4 data were superimposed onto the polygonal water supply map using Arcview GIS 3.2. This enabled linking of the two data sources, allowing us to add an estimated gestational exposure status to the T_4 levels measured in each newborn. It was not necessary to use GIS in the assessment of exposure in the control group from Hertzlia. This population was considered to be homogeneous with respect to exposure to perchlorate in drinking water.

Details on drinking water sources in pregnancy

Telephone interviews with mothers were done to assess actual exposure to perchlorate from drinking water. The question asked was "Which water did you usually drink during your pregnancy (including water for tea, coffee and concentrate)?" The options were "water from the tap," "filtered tap water," and "bottled water." Data were grouped for responses "tap water" and others.

This nonblinded telephone interview was conducted with all mothers in the very high and high exposure groups to determine their habits of drinking water during pregnancy (tap water or bottled water). A comparison of T_4 values was done between newborns in the very high and high exposure groups whose mothers drank tap water regularly during pregnancy.

Serum perchlorate concentrations from blood bank donors

To assess perchlorate exposure of the population residing in the three areas, serum samples of blood bank donors obtained during January 2003–September 2004 (before closing the well in the high exposure area) were identified from the Magen David Adom (MDA), National Blood Services, and the Israeli National Serum Bank. Perchlorate assay of these samples was done at the Centers for Disease Control (CDC), in a double-blind analysis. The usage of serum samples was approved by the Israeli Ministry of Health.

Serum perchlorate, thiocyanate, nitrate, and iodide were analyzed by using modifications to previously published methods (18,19). Briefly, 0.5 mL of serum was spiked with an isotopically labeled internal standard isotropically labeled perchlorate ($Cl^{18}O_4^-$), mixed, and incubated (2 minutes) to allow the internal standard to equilibrate into the sample. Subsequently, serum proteins were precipitated using six volumes of cold ($-20°C$) ethanol; thus protein-bound iodine was precipitated and only free iodide was measured. Samples were centrifuged ($3016 \times g$, $-5°C$) for 35 minutes. Supernatant was transferred to a clean centrifuge tube and evaporated to dryness under a stream of nitrogen at $60°C$. The sample was resuspended in 1.0 mL of deionized (DI) water and added to a preconditioned C18 SPE cartridge. The breakthrough fraction and a subsequent 1 mL wash of DI water were collected and mixed, and 1 mL was transferred to an autosampler vial. This solution was subsequently analyzed using ion chromatography–electrospray ionization–tandem mass spectrometry. Perchlorate was quantified based on the peak area ratio of analyte to stable isotope-labeled internal standard. Two quality control pools were analyzed in each analytical batch with unknown samples. Reported results met the accuracy and precision specifications of the quality control/quality assurance program of the Division of Laboratory Sciences, National Center for Environmental Health, CDC (similar to rules outlined by Westgard) (20). Excellent analytical precision was found when serum quality control pools were repetitively analyzed for perchlorate. Analytical response was linear across the calibration range (0.05–500 μg/L). Contamination was assessed by lot screening all reagents and analyzing blanks with each batch of unknowns; no contamination problems were identified.

Statistical analysis

Statistical analysis was done on SPSS 14. After checking for normal distribution, two-tailed t-tests were used to compare T_4 level means. In addition, analysis of variance (ANOVA) was used for mean comparisons with Bonferroni correction. Chi-square analysis was used for nonparametric data. Pearson correlation was utilized on linear data, and the Spearman Rho correlation was employed in nonparametric analysis. A matched control analysis between the high and low exposure groups was also done. $p < 0.05$ was considered statistically significant.

Results

There were 97 eligible newborns in the very high exposure group, 216 in the high exposure group, and 843 in the low exposure group. The concentrations of perchlorate in drinking water, demographic characteristics, birth weight, gestational age of newborns, maternal age, and corresponding neonatal T_4 levels in these three groups are shown in Table 1.

At the first stage of the study, T_4 levels obtained from the national NBS program for congenital hypothyroidism were

TABLE 1. PERCHLORATE EXPOSURE: DEMOGRAPHICS AND NEWBORN T_4 LEVELS

Perchlorate in drinking water ($\mu g/L$)[a]	n	Maternal age[a,b] Mean (SD)	Birth weight[a] (g) Mean (SD)	Gestational age[a] (week) Mean (SD)	T_4[a] ($\mu g/dL$) Mean (SD)	Gender (%)
Very high: Morasha (>340)[a]	97	31.2 (4.8)	3182 (516)	38.8 (2.2)	13.93 (3.8)	M 48.5 F 51.5
High:[a,b] Ramat Hasharon (42–94)	216	32.3 (4.3)[b]	3220 (454)	38.7 (3.5)	13.91 (3.4)	M 50.0 F 50.0
Low:[a] Herzlia (<3)	843	31.4 (4.6)	3228 (450)	39.0 (1.7)	13.98 (3.5)	M 54.3 F 45.7
Total	1156	31.6 (4.6)	3222 (457)	38.9 (2.2)	13.97 (3.5)	M 48.5 F 51.5
ANOVA	1156	$p = 0.046$[b]	NS $p = 0.648$	NS $p = 0.109$	NS $p = 0.952$	Chi-square NS $p = 0.336$

[a]Two-tailed t-tests assuming equal variances with Bonferroni correction revealed no significance in any of the parameters ($p > 0.05$).
[b]ANOVA maternal age significantly older in high exposure area (Bonferroni correction $p = 0.056$).

compared between newborns in the three groups. As shown in Table 1, there was no significant difference in T_4 levels between the groups as indicated by a p-value of 0.95. These T_4 values were normally distributed in each of the three groups (Fig. 2).

Residing in an area with a very high concentration of perchlorate in the drinking water does not necessarily denote high perchlorate consumption. Therefore, we further investigated the specific patterns of tap water use (e.g., drinking, cooking) during gestation by telephone interview, as an indicator of potential perchlorate exposure. Data on 31 mothers in the very high exposure group and 62 mothers in the high exposure group, who drank tap water, were compared with the low exposure group (Table 2). There were no statistically significant differences in T_4 levels between these groups.

In addition to perchlorate, we considered the effects of potential confounders on T_4 levels in the study population. Neonatal T_4 levels did not correlate with maternal age, birth weight, gestational age, or gender.

A matched control analysis was also done. Twenty-five newborns from the very high exposure area, whose mothers drank tap water and for whom there were complete data, were matched by gender, gestational age, and maternal age with
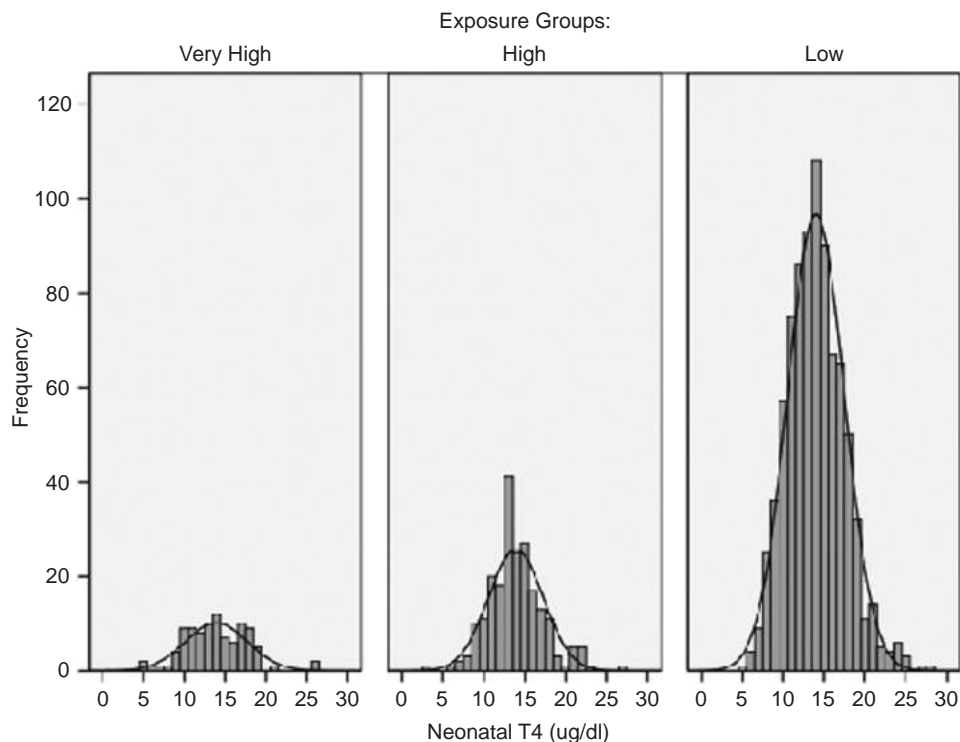

FIG. 2. Normal distribution of T_4 levels in the very high, high, and low exposure groups.

TABLE 2. MOTHERS AND NEWBORNS FROM THE HIGH AND INTERMEDIATE PERCHLORATE EXPOSURE GROUPS
WHO DRANK TAP WATER DURING PREGNANCY COMPARED WITH THE LOW EXPOSURE GROUP

Perchlorate in drinking water ($\mu g/L$)	n	Maternal age[a] Mean (SD)	Birth weight (g) Mean (SD)	Gestational age (week) Mean (SD)	T_4 ($\mu g/dL$) Mean (SD)	Gender (%)
Very high: (≤ 340) Morasha tap water	31	33.3 (4.9)	3177 (679)	37.8 (3.1)	14.48 (3.9)	M 45.2 F 54.8
High: (42–94) Ramat Hasharon tap water	62	32.3 (4.2)	3164 (519)	38.9 (2.2)	13.76 (3.4)	M 48.4 F 51.6
Low: (<3)[a] Herziliyah	843	31.4 (4.6)[a]	3228 (450)	39.0 (1.7)	13.98 (3.5)	M 54.3 F 45.7
Total	936	31.5 (4.6)	3222 (464)	39.0 (1.8)	13.99 (3.5)	M 53.6 F 46.4
ANOVA		$p = 0.035$[a]	NS $p = 0.699$	$p = 0.058$	NS $p = 0.640$	Chi-square NS $p = 0.418$

[a]Mothers in the low exposure area were significantly younger.

newborns in the low exposure group. The mean T_4 level of newborns in the very high exposure group was 14.7 (SD 4.2) $\mu g/dL$ and in the low exposure group was 13.5 (SD 3.4) $\mu g/dL$; again exposure did not prove to be a significant determinant of neonatal T_4 levels ($p = 0.271$).

Exposure assessment of the populations residing in the very high, high, and low exposure areas was further studied by a double-blind analysis of serum samples from blood bank donors residing in these areas. Figure 3 shows the serum perchlorate levels of blood donors from three proxy populations (residing in the areas corresponding to the three groups). As expected, the serum perchlorate levels of these three proxy populations fall into distinct clusters that correlated well with drinking water perchlorate concentrations from the same areas. Those with the highest serum perchlorate levels ($5.99 \pm 3.89 \mu g/L$) corresponded with the very high exposure group ($\leq 340 \mu g/L$ perchlorate in drinking water); those with high serum perchlorate levels ($1.19 \pm 1.37 \mu g/L$) corresponded to the high exposure group ($42–94 \mu g/L$ in drinking water); those

with the lowest serum levels ($0.44 \pm 0.55 \mu g/L$) corresponded to the controls ($<3 \mu g/L$ perchlorate in drinking water).

Among the blood donors, the difference between serum perchlorate levels of the high and low exposure groups was significant ($p = 0.04$). However, the difference between the very high and low exposure groups was marginally significant ($p = 0.06$), whereas the difference between the very high and high groups was not significant ($p = 0.09$). The lack of statistical significance between the very high and low exposure groups is obviously due to the small sample size in the very high exposure group ($n = 4$).

The potential for inhibition of iodide uptake by the thyroid gland depends on the relative levels of iodide and physiologically relevant competitive inhibitors of iodide uptake (perchlorate, nitrate, and thiocyanate). Therefore iodide, nitrate, and thiocyanate were measured along with perchlorate in the samples from blood donors residing in the combined very high/high (exposed) versus low perchlorate (control) areas. The values (mean $\pm$ SD) were as follows: nitrate, 4845 ± 217 and
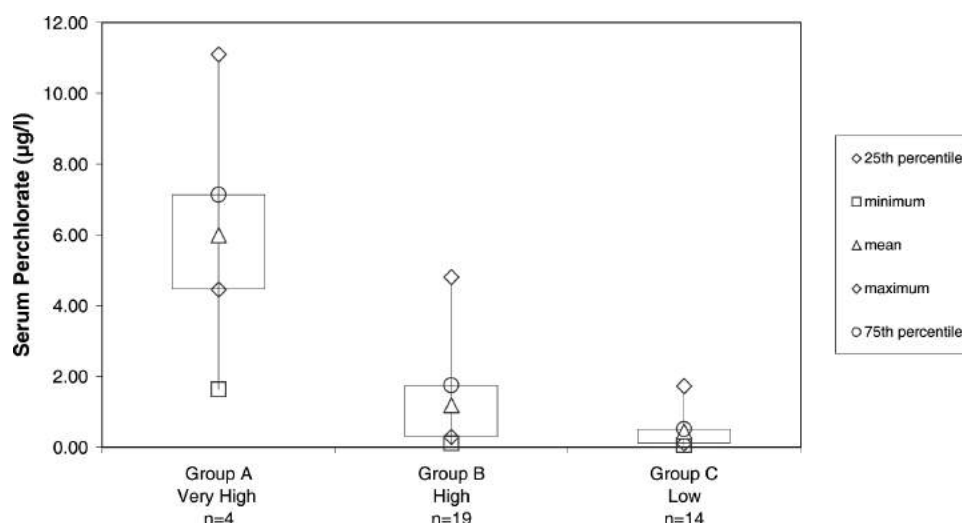

FIG. 3. Serum perchlorate levels of blood donors residing in areas corresponding to groups A (Morasha), B (Ramat Hasharon), and C (Herzlia/control) during 2003–2004.

$4661 \pm 1465\,\mu g/L$ ($p = 0.787$); thiocyanate, 1906 ± 1552 and $1067 \pm 1044\,\mu g/L$ ($p = 0.086$); iodide, 3.10 ± 1.25 and 2.24 ± 0.85 $\mu g/L$ ($p = 0.031$); and perchlorate, 1.97 ± 2.69 and 0.44 ± 0.55 $\mu g/L$ ($p = 0.045$), for the exposed and control populations, respectively. p-values are two-tailed.

Discussion

We report on the association between gestational exposure to perchlorate in drinking water and T_4 levels in newborns from Ramat Hasharon, Israel. Serum T_4 of newborns whose mothers drank water with perchlorate concentrations in the range of $42\,\mu g/L$ and above, up to the highest measured level of $340\,\mu g/L$, were similar to those of controls even after exclusion of those whose mothers reported drinking bottled water.

Additionally, serum perchlorate analysis was performed by the CDC on blood donors who resided in the three areas corresponding to various exposure levels. These levels, used as a proxy indicator of exposure, were well correlated with these three exposure groups. Despite likely differences between the proxy blood donors and the pregnant study participants, these proxy samples confirm elevated perchlorate exposure in the residents of Morasha and Ramat Hasharon. It should be noted that perchlorate exposure was measured in blood donors (adults), whereas our study population was pregnant women and their newborns. Our findings indicate that even though pregnant mothers consumed drinking water with perchlorate levels mostly in the range $42–94\,\mu g/L$ and in some at least up to the highest level measured, that is, $340\,\mu g/L$, their newborns presented with normal T_4 levels.

Other potential confounders that may affect T_4 were also measured in blood donors residing in the same areas of the exposed and control population. These donors, used as exposed and control proxy populations, had similar levels of serum thiocyanate and nitrate, while serum perchlorate and iodide levels were significantly elevated in donors residing in the high exposure area.

Iodine intake is important for protecting the thyroid from iodide uptake inhibitors, such as perchlorate. Blount et al. (21) recently found that perchlorate exposure is associated with decreased thyroid function in U.S. women with low urinary iodine. Higher serum iodide levels in the high perchlorate exposure area may modulate any perchlorate-induced inhibition of iodide uptake. A previous study of pregnant women in the coastal areas of Israel indicates iodine sufficiency (urinary iodine median $= 143\,\mu g/L$, mean $= 130\,\mu g/L$) (22) based on World Health Organization (WHO) criteria. Another important difference between the current work and the Blount et al.'s study is the study population: we examined thyroid function in neonates, while Blount et al. (21) studied adults and adolescents. Based on differences in iodine intake and life stage for the two studies, our findings do not contradict those of Blount et al. (21).

The critical concern regarding perchlorate contamination of drinking water is the level of exposure that might place sensitive populations at risk. Therefore, it is of the utmost importance to establish a RfD, that is, the dose in mg/(kg body weight · day) that can be tolerated for a lifetime without adverse health effects. The EPA's risk assessment on perchlorate from 2002 (6) was made prior to the appearance of the peer-reviewed publication of the Greer et al.'s (1) human exposure study, which showed that $7\,\mu g/(kg \cdot day)$ did not inhibit iodine uptake in healthy adults. A 10-fold safety factor to account for the most sensitive populations applied to this value resulted in the RfD of $0.7\,\mu g/(kg \cdot day)$ proposed by the NRC (2). Ultimately, the EPA also developed independently an RfD of $0.7\,\mu g/(kg \cdot day)$

from which they derived their DWEL of $24.5\,\mu g/L$. NRC recommended an RfD in February 2005. Gibbs (23) noted that $10\,\mu g/L$ perchlorate (converted from Gibbs' original data units of $\mu mol/L$) in serum corresponds to $6\,\mu g/(kg$ body weight · day). This value is very close to the NOEL of $7\,\mu g/(kg \cdot day)$ based on the clinical study of Greer et al. (1) and approximately 10-fold greater than the RfD of $0.7\,\mu g/(kg \cdot day)$ proposed by the NRC (2). In our study, serum perchlorate levels of nearly $6\,\mu g/L$ (Fig. 3) were found in subjects residing in the area corresponding to pregnant women in the high exposure group with $\leq 340\,\mu g/L$ perchlorate in their drinking water. If we assume a default drinking water consumption value of $2\,L/day$ (24), subjects in this group drank about $680\,\mu g/day$ of perchlorate. When we divide this value by the default body weight of $70\,kg$ (24), it is revealed that subjects in this group consumed approximately $9.7\,\mu g/(kg \cdot day)$ or 38.6% greater than the NOEL [$7\,\mu g/(kg \cdot day)$]. Similarly the high exposure group (drinking water perchlorate levels of $42–94\,\mu g/L$) extrapolates to doses of $1.2–2.7\,\mu g/(kg \cdot day)$, values less than the NOEL, but about 1.7–3.8 times higher than the RfD.

Keeping in mind the concern for fetal and neonatal development, there have been several human studies that testify to the lack of adverse affects in neonatal thyroid function from exposure to perchlorate in drinking water (8–12,25). Most of these considered perchlorate concentrations in the range 6–$16\,\mu g/L$, that is, lower than the DWEL of $24.5\,\mu g/L$.

Of the epidemiological studies examining thyroid function in neonates with perchlorate exposure, one ecological study by Brechner et al. (3) reported significantly higher median thyroid-stimulating hormone (TSH) levels in age-adjusted newborns attributed to perchlorate. However, this study was criticized by Goodman (13) and Lamm (14) on several grounds. Other cross-sectional studies of newborns in Chile and Nevada did not show the differences reported by Brechner et al. (3). Lamm (14) reevaluated the same sampling data used by Brechner et al. (3) and found that the differences they reported were regional differences and not due to exposure.

Women from Ramat Hasharon putatively consumed drinking water contaminated with typically $42–94\,\mu g/L$, and those from Morasha, $\leq 340\,\mu g/L$ (the highest measured level of perchlorate in drinking water) during pregnancy. These levels exceed any threshold value recommended to date and, to the best of our knowledge, rival the highest drinking water exposure levels reported during gestation. Despite these exposures, neonatal T_4 levels were in the range of normal and not different from those of infants born to mothers from areas where perchlorate levels were $< 3\,\mu g/L$.

Crump et al. (8) studied the effect of very high perchlorate exposure in drinking water ($100–120\,\mu g/L$) on thyroid function in schoolchildren. No difference was found in TSH levels or goiter prevalence among lifelong residents from this area compared with those living in a low exposure area (after adjusting for age, sex, and urinary iodine). No presumptive cases of congenital hypothyroidism were detected in those areas with very high to intermediate levels ($5–7\,\mu g/L$) of perchlorate in drinking water, whereas seven cases were detected in control area (perchlorate undetectable). Neonatal TSH levels were significantly lower in the highly exposed group compared with controls; this is opposite to the known pharmacological effect of perchlorate, and of small magnitude. Both our study and the Crump study (8) indicate that perchlorate in drinking water at concentrations as high as $100–120\,\mu g/L$ does not suppress thyroid function in newborns or school-age children, respectively. We note that perchlorate exposure levels in Ramat Hasharon ($48–92\,\mu g/L$) approach those in Taltal, Chile, and the serum

perchlorate levels in Ramat Hasharon (nd–6 μg/L) approach the serum perchlorate levels (2.2–8.9 μg/L) found in children in Taltal (26). In a more recent report of the same areas of Chile studied by Crump *et al*. (8), Tellez *et al*. (12) found comparable thyroid function during pregnancy and postpartum pregnant women from subjects exposed to various perchlorate concentrations.

The relative resistance of the thyroid gland to perchlorate exposure is most likely explained by normal homeostatic mechanisms of thyroid hormone metabolism. Inhibition of iodine uptake via the sodium/iodide symporter (NIS) is only the first step in a complex sequence of physiological events that regulate thyroid gland function (27), and it is reversible (28). Below the threshold for inhibition of iodine uptake, there would not be any effect, and some studies have indicated that TSH is not affected by long-term exposure to higher perchlorate levels (8,29). Lawrence *et al*. (30) showed that whereas daily consumption of 10 mg perchlorate for 2 weeks significantly decreased iodide uptake by the thyroid gland, neither circulating thyroid hormone nor TSH concentrations were affected. An occupational study of healthy male workers (29) showed that the thyroid can compensate for long-term exposure to perchlorate by increasing the efficiency of iodine uptake. In their physiologically based pharmacokinetic analysis of perchlorate inhibition of iodine uptake in the rat, Clewell *et al*. (31) emphasized that overall risk to the fetus may be less than to the neonate because during gestation the fetus can obtain thyroid hormones from the mother. According to Clewell *et al*. (31), "the maternal hormones may compensate for the increased inhibition seen in the fetal thyroid resulting in less chance of adverse developmental effects." However, the maternal–fetal T_4 transfer is not sufficient to prevent the effects of *in utero* hypothyroidism (18). This was demonstrated by very high TSH and the lack of epiphyseal nuclei in athyreotic newborns of euthyroid mothers (18).

A public health goal for perchlorate is prevention of its potential to cause neurodevelopmental deficits in newborns that might arise from maternal or neonatal hypothyroidism. More definitive evidence of the safety of gestational perchlorate exposure in Ramat Hasharon will require further study of neurobehavioral development in infants whose mothers were exposed to high perchlorate levels during pregnancy. In their ecological study of Nevada children, Chang *et al*. (32) found no evidence of increased risk of attention-deficit hyperactivity disorder or autism caused by perchlorate contamination of drinking water up to 24 μg/L (the DWEL proposed by the EPA). These authors also reported no differences in fourth-grade school performance. However, as recognized by Chang *et al*., there were limitations to their study pertaining to diagnostic criteria and the ability to ascertain geographic and demographic differences and, perhaps more importantly, to data on individual residence and water consumption during pregnancy. Such studies are important for Ramat Hasharon, where perchlorate contamination far exceeded that in Nevada.

In conclusion, our data and those of others (6–10,32) found no association between neonatal thyroid function and maternal consumption of drinking water that contains perchlorate at levels in excess of the DWEL (24.5 μg/L). Because this DWEL derives from the RfD, the perchlorate RfD of 0.7 μg/(kg · day) is likely to be protective of thyroid function in neonates of mothers with adequate iodine intake.

Acknowledgments

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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