Perchlorate in Drinking Water During Pregnancy and Neonatal Thyroid Hormone Levels in California

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Objective: To evaluate associations between maternal drinking water perchlorate exposure during pregnancy and newborn thyroid hormone levels. **Methods:** Elevation in thyroid stimulating hormone (TSH), which may reflect reduced thyroxin concentration, was assessed in 497,458 newborns in California in 1998. A total of 800 perchlorate water measurements were used to classify California communities as exposed (>5 μg/L) or unexposed. Results were stratified by age at TSH collection because of the normal postbirth TSH surge, and because water sources and perchlorate exposure can change soon after birth. **Results:** In TSH samples collected within 24 hours of birth, the odds ratio for a TSH greater than 25 μU/mL in exposed communities was 1.53 ($P < 0.0001$). After 24 hours, the odds ratio for a TSH more than the 95th percentile was 1.27 ($P < 0.0001$). **Conclusion:** These findings suggest that perchlorate is associated with increased neonatal TSH levels.

Perchlorate is an inorganic compound occurring both naturally and from manmade sources. It has been used as an oxidizer in solid rocket propellant, slurry explosives, and road flares.[1] Exposure appears to be widespread. In the 2001–2002 National Health and Nutrition Examination Survey (NHANES), perchlorate was detected in the urine of all 2820 US residents assessed.[2] Human exposure occurs through food or water. In a recent survey by the US Food and Drug Administration, perchlorate was found in 213 of the 286 foods tested.[3] And, in 2008, the US Environmental Protection Agency (EPA) estimated that as many as 16.6 million people in the United States may have been drinking water with perchlorate concentrations greater than 4 μg/L,[4] a level just below the California Public Health Goal (PHG) for perchlorate.[1] Perchlorate has contaminated many water sources in the United States including the Colorado River, which supplies a large fraction of all drinking water to Southern California.[5]

The toxic mechanism of perchlorate is competitive inhibition of the sodium-iodide symporter and subsequent inhibition of iodide uptake in the thyroid.[6] Iodide is a precursor of thyroid hormone, and at high doses perchlorate is known to decrease thyroid hormone production.[7] Several studies at lower exposures have not found clear associations between perchlorate and decreased thyroid hormone, but most of these were done in healthy adult volunteers or healthy workers who may not have been particularly susceptible to perchlorate.[8–11] However, recently an association was found between increasing urinary perchlorate concentrations and decreasing serum thyroid hormone levels in the 2001–2002 NHANES.[12] This finding was significant for two reasons. First, since NHANES is essentially a nationally representative sample, the perchlorate levels where the thyroid hormone effects were found are those that are commonly found in the general population (estimated median intake of 4 μg/day).[2] Second, the effects were greatest in women with low to moderate iodine levels, highlighting the importance of specifically examining potentially susceptible groups.

The developing fetus and young child may be particularly susceptible to perchlorate, since these are periods of rapid neurological development that are highly dependent on thyroid hormone.[1] These are also periods when thyroid hormone stores are low and a time when many infants may not be receiving adequate iodine intake.[13,14] It is well established that large decreases in thyroid hormone during pregnancy can cause severe mental and physical development abnormalities in the offspring. However, more recently several studies have linked even mild decreases in thyroid hormone levels to adverse effects on fetal brain development and childhood cognition.[15–20] These new findings highlight the potential importance of any chemical exposure that can affect thyroid function in the developing fetus and child.

In California, thyroid stimulating hormone (TSH) is measured in all newborns as part of a mandatory newborn screening (NBS) program.[21] This is usually done just before the newborn leaves the hospital. For normal uncomplicated vaginal deliveries, this is typically within 48 hours of birth. Perchlorate could reduce the production of thyroxine (T4), the major form of thyroid hormone. Decreases in T4 stimulate the pituitary to secrete TSH, which stimulates the thyroid to produce more T4. An increase in TSH is frequently used in screening programs as a marker for hypothyroidism, since an increased TSH is commonly successful in preventing marked decreases in T4 and thus can be a more sensitive marker of altered thyroid function than T4.

In this study, we investigate perchlorate-TSH associations using databases from California involving nearly 500,000 neonatal TSH levels and more than 800 perchlorate drinking water measurements. These same databases were used in a previous investigation, which found no association between perchlorate and primary congenital hypothyroidism (PCH).[22] PCH is generally a severe condition caused by a missing or underdeveloped thyroid gland and can lead to severe mental and physical growth retardation if not quickly treated with thyroid hormone.[23] The cutoff levels of TSH used to screen for PCH and trigger further testing are usually set fairly high. In California, the cutoff was 25 μU/mL, which is about the upper 99.9th percentile.[22] This was the cutoff used in the previous study in California.

The focus of the analysis we present here is different. Given the recent evidence discussed earlier linking even small changes in thyroid hormones to significant neurodevelopmental effects in children, we focused on changes in TSH that are less severe than those used to screen for PCH. We hypothesize that while relatively low levels of perchlorate may not be associated with PCH and large increases in TSH, they could be associated with the smaller changes in thyroid hormone that have still been associated with altered neurodevelopment.[15,17–20]

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METHODS

Neonatal TSH levels collected from January to December, 1998 as part of the California NBS Program were obtained from the California Department of Public Health (CDPH) (formerly the Department of Health Services). 1998 was the first full year in which California began testing all newborns for TSH and the second year of widespread perchlorate testing in California.[5] In addition to TSH, this data set included the following information on each newborn: gender, race/ethnicity, the number of hours after birth when blood samples for TSH measurements were collected ("collection age"), birth weight, mother's age, mother's residence (city and zip code), multiple-birth status, and feeding type (breast, formula, other). Subjects in this data set meeting the following criteria were excluded: (1) accession dates not within 1998; (2) missing TSH levels; (3) collection ages 0 or less or more than 999 hours; (4) second or greater multiple birth; (5) birth weight less than 250 or more than 7500 g; (6) duplicate entries; and (7) unknown gender. Further details on the NBS program are provided elsewhere.[22,24] This study has been approved by the University of California, Berkeley Committee for the Protection of Human Subjects.

Information on perchlorate concentrations in the municipal water sources in California for the years 1997 and 1998 were obtained from the CDPH's Drinking Water Program (DWP).[5] These years span the gestation period for children born in 1998. This data set included more than 800 perchlorate measurements on more than 200 separate water sources, and covered water sources supplying an estimated 66% of the state's population. The water distribution systems in many California communities are highly complex. Some communities are supplied by several water companies or municipal suppliers, each of which may obtain water from several water sources. These different sources may have different perchlorate concentrations, and the amount of water obtained from each source can change from day to day. Because of this complexity, we did not attempt to assign a single perchlorate concentration to each California community, but rather, categorized communities into one of two groups on the basis of whether their estimated average perchlorate concentrations were more than ("exposed") or less than ("unexposed") 5 μg/L. This level was chosen because it was used in the previous study, and because it is near the California detection limit for reporting of 4 μg/L and the current California perchlorate regulatory standard of 6 μg/L.[5] The same communities defined as exposed (>5 μg/L) in the previous study were defined as exposed in this analysis, and details of the exposure assignment methods were described previously.[22] Briefly, information on each city or town served by each water system tested by the DWP was collected from either the DWP file or through Internet searches or telephone interviews collected by the initial research staff. The average water system perchlorate concentration was calculated as the arithmetic mean of the median concentrations from each contributing water source. The perchlorate concentration in each community in California was then estimated as the average of the concentrations of the different water systems supplying that community, weighted by the number of water sources used by each system. In this analysis, communities with estimated average perchlorate concentrations of 5 μg/L or less and all communities in California without any perchlorate measurements were defined as "unexposed." Because of the widespread attention perchlorate has received in California, it was deemed highly unlikely that communities without perchlorate measurements had widespread high perchlorate exposure. Regardless, removing communities without perchlorate measurements from the unexposed group had little impact on results. Other methods were also assessed to classify exposure. For example, analyses were performed, in which any community with at least two separate water sources with perchlorate concentrations greater than 4 μg/L was defined as "exposed." This had only small impacts on results.

Several statistical analyses were done. First, bivariate analyses were done to investigate associations between TSH levels and sociodemographic factors such as gender, race/ethnicity, feeding type, mother's age, income, and birth weight. Since TSH levels were not normally distributed, geometric means were calculated and differences between groups were assessed using the Wilcoxon rank-sum test. Bivariate analyses were also done to assess associations between these sociodemographic factors and perchlorate exposure using either unadjusted odds ratios (ORs) or the t -test when variables were normally distributed.

Logistic regression was used to calculate ORs for having a high TSH, comparing perchlorate-exposed and unexposed communities. Initially, the cutoff point for defining a high TSH was set at 25 μU/mL, since this was used in the previous study. However, to evaluate more subtle effects, lower cutoff points, including the upper 95th percentiles, were also used. The 95th percentile is near the maternal levels of T4 and TSH that have been associated with significant neurodevelopment effects in the studies discussed earlier.[15,17–20] Using logistic regression, we calculated both unadjusted ORs and ORs adjusted for gender, race/ethnicity (Asian, Black, Hispanic, White, other, and unknown, each coded as 0 or 1), birth weight (entered as less than or more than the 5th or 95th percentiles, respectively, each coded as 0 or 1), feeding type (each type entered as 0 or 1), mother's age (entered as less than 19 or more than 32 years, as 0 or 1), the per capita income of the zip code where the mother resided (each quartile entered as 0 or 1), and collection age (as described later). Entering birth weight and mother's age as continuous variables or in quartiles had little impact on results. Data on per capita income for each zip code in California were obtained from the 2000 US Census and matched to the residential zip code of the mother provided in the NBS data set.[25]

Neonatal TSH levels normally surge within the first few hours after birth, peaking at about 2 hours after birth and steadily decreasing to normal long-term levels over the next 48 to 72 hours.[26,27] Because of this surge, collection age is a strong determinant of neonatal TSH levels. We addressed potential confounding or effect modification due to this surge in several ways. First, because the surge occurs mostly within the first 24 hours of birth, all analyses were stratified on the basis of whether the collection age was greater or less than 24 hours. Second, possible residual confounding was addressed by adjusting for collection age within each of these strata. This was done by dividing collection age into five categories: 0 to 5 hours (the period of early very unstable TSH values), 6 to 19 hours (the period when mean TSH levels peaked in this data set), 19 to 32 hours (the period when TSH levels decline rapidly), 33 to 70 hours (the period when TSH levels decline more slowly), and 70 hours or more (the period when TSH levels are close to long-term levels). Each of these periods was entered as a dummy variable in the logistic regression model. Categorizing collection age into two-, four-, or six-hour intervals, or as a continuous variable (by hour), had little impact on results. Finally, adjusted ORs were calculated for each hour of collection age, using the 95th percentile of TSH for each hour as the cutoff point for defining a high TSH. Five-hour average OR estimates, centered on the hour of interest, are presented for each hour to reduce fluctuations from small numbers. All statistical analyses were done using SAS version 9.1.2 (Cary, NC), and all P values are two-sided.

In addition to the different TSH cutoff points, the differences between this study and the previous analysis of these data are as follows: (1) minor differences in the way potential confounders were categorized and entered into logistic regression models; (2) minor differences in exclusion criteria; (3) we adjusted for per capita income, whereas the previous analysis did not; and (4) our inclusion of communities without perchlorate measurements into the "unexposed" group. As we show, none of these differences had any important effect on the results.

TABLE 1. Number of Subjects Excluded and the Reasons for Exclusion

Reason for Exclusion	Number Excluded	Remaining Subjects
Total entries received	–	543,986
Accession dates not in 1998	32,671	511,315
TSH missing	3	511,312
Collection age ≤0 or >999 hr	961	510,351
Multiple birth	6,671	503,680
Birth weight <250 or >7500 g	4,499	499,181
Duplicate entry	1,340	497,841
Gender unknown	383	497,458
Total excluded	46,528	

RESULTS

The initial data set received from CDPH contained 543,986 entries. Of these, 46,528 were excluded for the reasons given in Table 1,leaving a total of 497,458 subjects. Among active wells in the 1997–1998 DWP data set with perchlorate concentrations more than the detection limit for reporting (4 μg/L), the median perchlorate concentration was 7.9 μg/L, with a high of 159 μg/L. The overall geometric mean TSH in all neonates combined was 4.06 μU/mL (SD = 5.75 μU/mL) (Table 2).The upper 95th percentile TSH values for collection ages before and after 24 hours were 15 μU/mL and 8 μU/mL, respectively. As seen in Table 2, mean TSH levels were higher in males (4.21 μU/mL) than in females (3.91 μU/mL), higher in Asians (4.40 μU/mL) than other ethnicities (4.01 to 4.15 μU/mL), and higher with normal birth weights (4.18 μU/mL) than birth weights more than or less than the 95th and 5th percentiles (3.76 μU/mL and 2.29 μU/mL, respectively).

Table 3 shows the differences between perchlorate-exposed and unexposed communities. Compared with unexposed communities, exposed communities had a smaller proportion of Whites (OR = 0.57; 95% confidence interval [95% CI], 0.56 = 0.59) and Asians (OR = 0.59; 95% CI, 0.57 to 0.62) than Hispanics, a greater proportion of infants who were formula-fed (OR = 1.95; 95% CI, 1.90 to 2.00) versus breast-fed, and a smaller proportion of subjects in the lowest (OR = 0.86; 95% CI, 0.84 to 0.88) and highest per capita income quartiles (OR = 0.38; 95% CI, 0.36 to 0.39).

For neonates with collection ages less than 24 hours, the adjusted OR for having a TSH of 25 μU/mL or greater was 1.53 (95% CI, 1.24 to 1.89; $P < 0.0001$) comparing perchlorate-exposed to unexposed communities (Table 4).The corresponding OR for TSH levels at or above the 95th percentile for this collection age stratum (15 μU/mL) was 1.23 (95% CI, 1.16 to 1.31). The statistical adjustments had little impact on results. For example, the adjusted and unadjusted ORs for having a TSH of 25 μU/mL or greater for collection ages less than 24 hours were 1.53 and 1.52, respectively. For neonates with collection ages less than 24 hours, the ORs were higher in breast-fed infants than in formula-fed infants (eg, ORs for a TSH of 25 μU/mL or greater of 1.59 in breast-fed infants versus 1.24 formula-fed infants). Confining analyses to birth weights between 2500 and 4000 g, or excluding those with collection ages less than 4 hours (the period when TSH levels peak in healthy children) or very high TSH levels (ie, >200 μU/mL), also had little effect on results. Defining exposed communities as those with at least two separate water sources with perchlorate concentrations greater than 4 μg/L resulted in an additional nine exposed communities, and gave ORs that were similar to those reported earlier. For example, the OR for having a TSH of 25 μU/mL or greater for collection ages less than 24 hours using this exposure categorization method was 1.67 (95% CI = 1.37 to 2.00) (not shown in tables).

TABLE 2. Geometric Mean TSH Levels by Sociodemographic Characteristics

		Geometric		
	n	Mean	SD	*P*
Total	497,458	4.06	5.75	–
Females	243,285	3.91	6.34	Ref
Males	254,173	4.21	5.13	<0.001
Race/ethnicity				
Hispanic	241,357	4.01	6.28	Ref
Non-Hispanic	256,101	4.10	5.21	<0.001
White	148,009	4.01	5.21	0.04
Asian	43,355	4.40	6.01	<0.001
Black	31,600	4.15	3.95	<0.001
Other/unknown	33,137	4.05	5.14	0.004
Birth weight (percentile)				
Low (<5th)	20,853	2.29	9.43	<0.001
Medium (5th–95th)	451,666	4.18	5.50	Ref
High (>95th)	24,939	3.76	5.88	<0.001
Type of feeding				
Breast-fed only	212,112	4.19	5.21	Ref
Formula-fed only	85,035	4.12	6.10	<0.001
Both breast- and formula-fed	178,508	4.02	5.65	<0.001
Other/unknown	21,803	3.00	9.17	<0.001
Mother's age (yr)				
12–18	28,272	4.38	5.78	<0.001
19–32	331,729	4.15	5.80	Ref
>32	126,126	3.78	5.22	<0.001
Unknown	11,331	3.87	8.93	<0.001
Age at TSH collection (hr)				
0–5	3,224	5.11	5.46	<0.001
6–19	118,462	7.52	6.23	<0.001
20–32	194,708	4.38	4.57	<0.001
33–70	147,026	2.76	4.43	<0.001
>70	34,038	1.56	8.87	Ref
Per capita income quartiles ($/yr)				
<13,547	120,593	4.02	6.07	Ref
13,547–17,809	119,216	4.21	6.03	<0.001
17,810–25,373	119,957	4.04	5.19	0.003
>25,373	119,839	3.95	5.30	<0.001
Unknown	17,853	4.17	7.84	<0.001

Ref, reference group.

For neonates with collection ages of 24 hours or greater, the OR for having a TSH of 25 μU/mL or greater was 0.72 (95% CI, 0.41 to 1.27), although only 13 subjects from exposed communities had a TSH more than this level (Table 5).The corresponding OR for a TSH level at or above the 95th percentile (8 μU/mL) was 1.27 (95% CI, 1.22 to 1.33; $P < 0.0001$; $n = 2711$ neonates from perchlorate-exposed communities with a TSH of 8 μU/mL or greater). This OR remained elevated in analyses stratified by gender, race/ethnicity, and feeding type, and after excluding high and low birth weights and extreme TSH values. Adjustments had only small impacts on these results as well. For example, the adjusted and unadjusted ORs for all subjects with collection ages of 24 hours or greater for having a TSH of 8 μU/mL or greater were 1.27 and 1.31, respectively. Per capita income had little effect on results. In an analysis limited to only those neonates from the second lowest per capita income quartile (the most common one among exposed communities), the adjusted OR for having a TSH of 8 μU/mL or greater comparing exposed to unexposed communities was 1.31 (95% CI, 1.21 to 1.41).

TABLE 3. Demographic Characteristics by Perchlorate Exposure Category

	Perchlorate Exposure Category					
	≤5 μg/L		>5 μg/L			
Variable	***n***	**%**	***n***	**%**	**OR (95% CI)∗**	***P*†**
Total	451,708	–	45,750	–		
Males	230,955	51.1	23,218	50.7	0.98 (0.97−1.00)	
Females	220,753	48.9	22,532	49.3	1.00 (Ref)	
Race/ethnicity						
Hispanic	214,027	47.4	27,330	59.7	1.00 (Ref)	
White	137,926	30.5	10,083	22.0	0.57 (0.56−0.59)	
Asian	40,301	8.9	3,054	6.7	0.59 (0.57−0.62)	
Black	28,608	6.3	2,992	6.5	0.82 (0.79−0.85)	
Other/unknown	30,846	6.8	2,291	5.0	0.58 (0.56−0.61)	
Birth weight (percentile)						
Low (<5th)	18,890	4.2	1,963	4.3	1.02 (0.97−1.07)	
Medium (5th−95th)	409,948	90.8	41,718	91.2	1.00 (Ref)	
High (>95th)	22,870	5.1	2,069	4.5	0.89 (0.85−0.93)	
Mean (g) (SD)	3,375	(571)	3,357	(570)		<0.001
Type of feeding						
Breast-fed only	197,729	43.8	14,383	31.4	1.00 (Ref)	
Formula-fed only	74,483	16.5	10,552	23.1	1.95 (1.90−2.00)	
Both breast- and formula-fed	159,614	35.3	18,894	41.3	1.63 (1.59−1.66)	
Other/unknown	19,882	4.4	1,921	4.2	1.33 (1.26−1.40)	
Mother's age (yr)						
12−19	25,419	5.6	2,853	6.2	1.06 (1.02−1.11)	
19−32	300,030	66.4	31,699	69.3	1.00 (Ref)	
>32	116,016	25.7	10,110	22.1	0.82 (0.81−0.84)	
Unknown	10,243	2.3	1,088	2.4	1.01 (0.94−1.07)	
Mean (yr) (SD)	28.1	(6.3)	27.5	(6.2)		<0.001
Range	12−48	–	12−48	–	–	
Collection age (hr)						
Mean (SD)	36.8	(52.5)	36.1	(52.5)		0.008
Range	1−999	–	1−999	–	–	
Per capita income quartiles ($/yr)‡						
<13,547	108,575	24.0	12,018	26.3	0.86 (0.84−0.88)	
13,547−25,373	211,891	46.9	27,282	59.6	1.00 (Ref)	
>25,373	114,305	25.3	5,534	12.1	0.38 (0.36−0.39)	
Unknown	16,937	3.7	916	2.0	0.42 (0.39−0.45)	
TSH level						
Geometric mean (SD)	4.03	(5.84)	4.35	(4.83)	*P*	<0.001
Range	1−779	–	1−315	–	–	

CI, confidence interval; OR, odds ratio; Ref, reference group.
∗The odds ratio in the perchlorate-exposed communities compared with the unexposed communities.
†All *P* values use the *t* test except the analysis of TSH, which uses the Wilcoxon rank sum test.
‡The middle two quartiles were combined and used as the reference category.

Figure 1 shows the adjusted ORs for a TSH level equal to or above the hour-specific 95th percentile TSH comparing exposed and unexposed communities, plotted for each hour of collection age (as explained in the methods section, each OR in this figure is a 5-hour average centered on the hour of interest). For each hour shown, ORs are more than 1.0. After hour 65 (data not shown), ORs become unstable and confidence intervals become very wide because of the small number of exposed subjects, and hourly ORs after this time fluctuate widely.

DISCUSSION

Overall, the elevated ORs of 1.53 ($P < 0.0001$) and 1.23 ($P < 0.001$) for TSH levels of 25 and 15 μU/mL or greater respectively, within the first 24 hours of birth, and the elevated OR of 1.27 ($P < 0.0001$) for TSH levels of 8 μU/mL or greater after 24 hours of birth in exposed versus nonexposed communities all suggest that perchlorate in drinking water could be associated with increased neonatal TSH. Elevations of TSH are an indicator of thyroid stress and decreased T4 production.[1] The low *P* values for these findings show that they are unlikely due to chance. If these effects are real, these ORs suggest that exposure to perchlorate could cause about a 23% to 57% increase in the number of neonates with a high TSH, an increase that may be important given the widespread, ubiquitous nature of perchlorate exposure.[2]

The OR for TSH levels of 25 μU/mL or greater in subjects with collection ages 24 hours or greater was not elevated

TABLE 4. Adjusted Odds Ratios* for a High TSH Comparing Perchlorate-Exposed (>5 μg/L) and Unexposed Communities (≤5 μg/L): Collection Age 24 Hours or Less

	TSH ≥ 25†			TSH ≥ 15†		
	N	**OR**	**95% CI**	***N***	**OR**	**95% CI**
All subjects	102	1.53	1.24–1.89	1217	1.23	1.16–1.31
Gender						
Males	41	1.48	1.06–2.07	575	1.23	1.13–1.35
Females	61	1.57	1.19–2.07	642	1.23	1.13–1.34
Race/ethnicity						
Hispanic	57	1.56	1.17–2.09	657	1.19	1.09–1.30
Non-Hispanic	45	1.53	1.12–2.09	560	1.29	1.18–1.42
Type of feeding						
Breast-fed only	33	1.59	1.10–2.29	427	1.35	1.22–1.50
Formula-fed only	22	1.24	0.78–1.98	279	1.11	0.97–1.27
Both breast- and formula-fed	44	1.82	1.31–2.53	472	1.20	1.08–1.32
Other/unknown	3	0.67	0.20–2.20	39	1.37	0.96–1.96
Other analyses						
Birth weight 2500–4000 g	91	1.59	1.27–2.00	1095	1.23	1.15–1.32
Exclude collection ages <4 hr	101	1.59	1.29–1.97	1206	1.24	1.16–1.32
Exclude TSH >200 μU/mL	101	1.57	1.26–1.94	1216	1.23	1.16–1.32
Second lowest income quartile‡	50	2.11	1.53–2.91	460	1.25	1.13–1.39
Collection age: 2-hr categories§	102	1.61	1.30–1.99	1217	1.29	1.21–1.38

CI, confidence interval; OR, odds ratio; *N*, number of exposed cases.
*Adjusted for gender, race/ethnicity, birth weight, food type, mother's age, per capita income, and collection age.
†A TSH of 25 μU/mL is commonly used for PCH screening, and a TSH of 15 μU/mL is the upper 95th percentile of all TSH samples collected before 24 hours of age.
‡Includes only subjects in this quartile of per capita income.
§ Collection age was entered into the logistic regression model as dummy variables for each 2-hour category.

TABLE 5. Adjusted Odds Ratios* for a High TSH Comparing Perchlorate-Exposed (>5 μg/L) and Unexposed Communities (≤5 μg/L): Collection Age Greater Than 24 Hours

	TSH ≥ 25 μU/mL†			TSH ≥ 8 μU/mL†		
	***N*†**	**OR**	**95% CI**	***N***	**OR**	**95% CI**
All subjects	13	0.72	0.41–1.27	2711	1.27	1.22–1.33
Gender						
Males	3	0.44	0.14–1.40	1578	1.29	1.22–1.37
Females	10	0.89	0.46–1.71	1133	1.24	1.16–1.33
Race/Ethnicity						
Hispanic	9	0.70	0.35–1.38	1426	1.25	1.17–1.32
Non-Hispanic	4	0.74	0.27–2.04	1285	1.30	1.22–1.38
Type of feeding						
Breast-fed only	3	0.55	0.17–1.78	863	1.31	1.22–1.42
Formula-fed only	3	0.63	0.19–2.06	664	1.32	1.20–1.44
Both breast- and formula-fed	6	0.87	0.37–2.01	1108	1.21	1.13–1.29
Other/unknown	1	0.79	0.10–6.10	96	1.33	1.06–1.67
Other analyses						
Birth weight 2500–4000 g	12	0.87	0.48–1.57	2341	1.29	1.23–1.35
Exclude TSH >200 μU/mL	10	0.75	0.39–1.43	2708	1.27	1.22–1.33
Second lowest income quartile‡	6	1.19	0.49–2.87	968	1.31	1.21–1.41

CI, confidence interval; OR, odds ratio; *N*, number of exposed cases.
*Adjusted for gender, race/ethnicity, birth weight, food type, mother's age, per capita income, and collection age.
†A TSH of 25 μU/mL is commonly used for PCH screening, and a TSH of 8 μU/mL is the upper 95th percentile of all TSH samples collected after 24 hours of age.
‡Includes only subjects in this quartile of per capita income. This was the most common per capita income quartile among exposed communities.

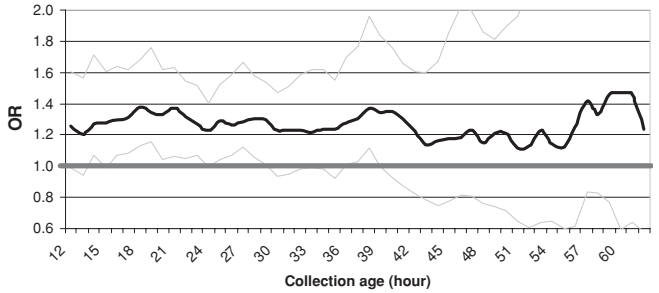

FIGURE 1. Adjusted odds ratios for having a TSH greater than or equal to the hour-specific 95th percentile comparing perchlorate-exposed (>5 μg/L) to unexposed communities (≤5 μg/L). The dark lines are the odds ratios, the upper and lower lighter lines are the upper and lower 95% confidence intervals. The blue line highlights an OR of 1.0. The estimates for each hour are 5-hour averages centered on the hour of interest.

(OR = 0.72; 95% CI, 0.41 to 1.27), and this result is similar to that reported in the previous analysis of these data (OR = 0.73; 95% CI, 0.40 to 1.23). Since a TSH level of 25 μU/mL is very high (>99.9)th percentile of all TSH samples collected after 24 hours of age), this result may mean that low environmental levels of perchlorate are not associated with extremely large increases in TSH. However, since the number of subjects with TSH levels of 25 μU/mL or greater was small ($n = 13$ exposed neonates), the statistical power of this particular analysis was low.

The exposure categorization in this study is based on ecologic data and there is likely some exposure misclassification because of the use of other water sources, incomplete perchlorate testing, or perchlorate in food. However, since thyroid hormone data were collected similarly, regardless of perchlorate exposure, the misclassification bias is most likely nondifferential and toward the null.[28] Thus, correcting for this bias would most likely increase the ORs identified here.

The positive effects identified in this analysis could be due to confounding, although an obvious strong confounder is not apparent. Several of the strongest known determinants of neonatal TSH (collection age, gender, birth weight, and race/ethnicity) were adjusted for and these adjustments had little impact on results. Factors such as nitrate, thiocyanate (usually from smoking or certain foods), and low iodine can also decrease T4 levels and increase TSH. Like perchlorate, thiocyanate and nitrate also competitively inhibit iodide uptake in the thyroid.[29] Importantly though, to cause significant confounding, these factors would have to be associated with both thyroid hormones and perchlorate exposure, and these associations would have to be fairly strong.[30] There is no evidence to suggest that these factors were strongly enough related to both perchlorate and TSH in this study to cause the effects identified. For example, while very high nitrate intakes have been associated with goiter, more common exposures have been linked with only weak or no effects on thyroid hormone levels.[31,32] In addition, high nitrate levels are usually found in rural and agricultural areas, not in the more urban areas like most of the perchlorate-exposed communities in this study.[33] In the two largest perchlorate-exposed communities, San Bernardino and Riverside, drinking water nitrate levels have been well below the California nitrate PHG.[34,35] Iodine levels are not specifically available for the perchlorate-exposed communities in this study. However, data show that iodine intake is related to race, age, the type of infant feeding, and gender, four factors that were adjusted for here and had little effect on results.[14,36]

The findings of this study are biologically plausible in that they are consistent with the known mechanism of perchlorate.[1] The low-dose effects seen here are consistent with data suggesting that the fetus and young children are susceptible to perchlorate in particular and environmental chemicals in general. Susceptibility factors include their low reserves of T4 (suggesting they are less able to respond to transitory decreases in T4 production),[13] the potentially large number of infants with low iodine intake,[14] an increased chemical intake per body weight compared with adults, rapid organ development, and underdeveloped metabolic and detoxification systems.[37] Several of the previous studies of perchlorate and thyroid hormone that found no associations were done in small numbers of healthy adult workers or volunteers.[8–11] Because of the small numbers, these studies likely included few, if any, people with low iodine or any other important susceptibility factor. It is possible that the reason these studies did not find associations similar to those reported in this study is because they did not specifically include susceptible groups.

Other studies in potentially susceptible groups support the findings of this study. As discussed, evidence of a linear association between increasing urinary perchlorate and decreasing serum T4 were identified in women in NHANES with low iodine and high thiocyanate exposures, and median perchlorate intakes of about 4 μg/day.[12,38] In Arizona, neonatal TSH levels were higher in perchlorate-exposed Yuma (water levels about 6 μg/L) compared with unexposed Flagstaff.[39] A reanalysis using a different "unexposed" comparison town found no difference in TSH levels compared with Yuma. However, this town was much smaller and only a few miles from Yuma, and the possibility that mothers from this town either worked, consumed food or water, or gave birth in Yuma was not explored.[40] If any of these occurred, the "unexposed" mothers and their neonates may have actually been exposed and results would be biased toward the null. In California, Kelsh et al[24] reported an OR of 1.24 (95% CI, 0.89 to 1.68; all TSH collection ages combined) for having a TSH greater than 25 μU/mL in neonates from Redlands, a city with high perchlorate levels in some wells (range, nondetectable to above 100 μg/L). The magnitude of this OR is close to the corresponding OR of 1.31 ($P < 0.0001$) identified in our study when all TSH collection ages were combined. Although not reported in their paper, the unadjusted OR in samples collected before 18 hours of age can be calculated using the data from their tables and was 1.57 (95% CI, 1.14 to 2.16), which is similar to the OR of 1.53 identified in our study. In both the Redlands study and the Arizona study, the unadjusted ORs for having a low T4 (generally less than 9 μg/dL) were also elevated, with very low P values (Redlands: OR = 1.18, $P < 0.0001$; Arizona: OR = 1.18, $P = 0.006$), suggesting that perchlorate exposure in these studies was associated with an almost 20% increase in the number of children with a low T4 (all of these calculations can be found at http://asrg.berkeley.edu/research.html).

Two studies from the same areas in Chile found no association between perchlorate water concentrations near 100 μg/L and neonatal thyroid hormone levels.[41,42] There was a marked overlap in urinary perchlorate concentrations between "exposed" and "unexposed" mothers, and 45% of the "exposed" neonates were actually born in the unexposed city. Since the half-life of perchlorate is short (about 8 hours),[10] these "exposed" infants may have actually been unexposed at the time of their thyroid hormone collection. Also, urinary iodine levels in this study were very high (three times US levels), which may have afforded some protection from perchlorate. In fact, only 16 women in this study had urinary iodine concentrations less than 100 μg/L, the level where the perchlorate-T4 association was strongest in NHANES.[12,43] In NHANES, 37% of US women had iodine concentrations less than 100 μg/L. Interestingly, the OR for a history of thyroid disease among older family members in the Chile study was elevated in the exposed city (OR = 4.97; 95% CI, 1.29 to 19.2). Prior to the 1980s (when Chile first began oversupplementing its salt with iodine), the iodine levels in Chile were very low and rates of goiter were high.[44] The authors hypothesized that this high OR

for a family history of thyroid disease might have been an effect of perchlorate in older family members during the low-iodine period.[41]

Several other studies in neonates and pregnant women have been negative. In Israel, no association was seen between neonatal thyroid hormone levels and residential drinking water perchlorate concentrations near 300 μg/L,[45] although there were only 31 mothers in this high exposure group. It is unknown whether the infants in this study consumed formula or whether mothers consumed drinking water from the hospital that had a different perchlorate concentration than their residential supply. Given the short half-life of perchlorate, either of these could have biased results toward the null. Two studies of urinary perchlorate concentrations and thyroid hormone levels in pregnant women have also been negative.[42,46] These findings are not necessarily inconsistent with the NHANES findings discussed earlier in nonpregnant women, since iodine levels were three times higher[42] or thiocyanate levels were five times lower[46] in these studies than the iodine and thiocyanate levels in those women in NHANES where perchlorate-T4 effects were strongest. As discussed earlier, iodine and thiocyanate may be important effect modifiers of perchlorate. Smoking is a major source of thiocyanate exposure in the United States, and data suggest that tobacco smoke exposure and thus thiocyanate levels are fairly high in pregnant women in California. In one large study, 62% of California pregnant women had detectable cotinine concentrations (a biomarker of tobacco smoke exposure) and 12% had cotinine levels consistent with active smoking.[47]

In this study, elevated ORs were seen with collection ages before and after 24 hours. Several previous studies involving neonatal thyroid hormone measurements excluded TSH measurements collected during the first 24 hours after birth. The reason given is that the early TSH surge can cause a high false-positive rate for PCH screening.[22,24,48] However, excluding these subjects from studies of chemical exposures is not routine.[42,49] This is because the goal of many studies, including ours, is not PCH screening. Instead, the goal is to simply evaluate whether there is a difference in TSH levels between exposed and unexposed subjects. This goal includes examining changes in TSH that are less severe than those associated with PCH. If PCH is the only outcome assessed, less severe effects might be missed. Because of this, methods that are designed solely to evaluate the effectiveness of PCH screening (like the calculation of PCH false-positive rates) are not appropriate for assessing the validity of this study or many other studies of chemical exposures and neonatal thyroid hormones. Another reason for not excluding TSH measurements within the first 24 hours of birth is that thyroid hormones during this period may be critically important in the health of many children. Worldwide, millions of infants die within the first 24 hours of birth, and decreases in T4 has been linked with increases in infant death.[50,51]

In fact, the first 24 hours after birth may be the best time to examine the impact of maternal perchlorate exposure on neonatal thyroid hormone levels. This is because perchlorate exposure can change after birth, for example, through the use of infant formulas (which contain highly variable perchlorate concentrations)[14,52] or water from the birthing hospital (in breast-fed infants) that can potentially have much different perchlorate concentrations than the mother's residential drinking water. In these cases, the mother's residential drinking water perchlorate concentration will no longer be an accurate indicator of the neonate's true exposure. These changes in exposure at birth would most likely cause a nondifferential misclassification and bias ORs toward the null.[28] Since the half-life of perchlorate and neonatal thyroid hormones is fairly short (about 8 to 24 hours),[10,13] this bias would likely become strongest after 24 hours after birth. This bias could explain why our study (for TSHs > 25 μg/L) and four others' found greater effects during the first 24 hours of birth than later.[24,39,41,53] It may also explain why some studies that excluded or had few measurements within the first 24 hours of birth did not report positive effects.[45,48] Further research is needed to explore this issue.

The exact long-term health consequences of the findings of this study are unknown. However, alterations in thyroid hormone have been linked to many adverse outcomes, including increases in infant mortality, adverse neurodevelopment and IQ effects, altered lipid metabolism, hypertension, cardiovascular disease, and adverse impacts on the kidney and lung.[1,51] This wide variety of effects highlights the complex and diverse role that thyroid hormone plays in human health. The results of several studies suggest that some of these adverse effects can occur with changes in thyroid hormone levels that were previously considered small and insignificant (eg, 10% to 20% changes in TSH or T4), and changes in thyroid hormone levels that occur within normal reference ranges.[15,17,18,20,54,55] Given this, and given the integral role thyroid hormone plays in many complex and important physiological systems, a reasonable public health approach might be to reduce any unnecessary stress on the thyroid system or any unnecessary change in thyroid hormones, including the types of perchlorate-associated changes identified in this study.

It might be argued that relatively small changes in thyroid hormone levels (eg, a 10% decrease in T4 or 10% increase in TSH) in an otherwise healthy individual might not cause overt disease, and therefore are unimportant. However, small average changes can be important at population extremes.[56] A classic example of this has been demonstrated with lead and IQ. A mean toddler blood lead of 15 μg/dL would be expected to decrease population IQ by more than five points. While a five-point loss of IQ might not be detectable in an otherwise healthy child, a 5% shift at the tails of the population distribution would result in a 57% increase in those classified as mentally retarded (IQ < 70) and a 57% decrease in those classified as gifted (IQ > 130).[56] Relatively small, but widespread, changes in thyroid hormone levels could potentially have similar adverse population impacts.[56]

In conclusion, the results of this study provide some evidence that perchlorate exposure is associated with increased TSH levels in neonates, and highlight the importance of investigating effects in potentially susceptible groups, such as young children. The effects identified in this study could potentially have important public health effects, given the importance of thyroid hormone and the large number of people exposed to perchlorate. However, currently it is unknown whether the effects seen here cause actual impacts on health and development. Further research is needed on this issue, and needed to evaluate the possible role that iodine, thiocyanate, nitrate, and other thyroid-active agents may have played in these findings.

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