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ORIGINAL ARTICLE

Thyroid hormones and thyroid disease in relation to perchlorate dose and residence near a superfund site

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Perchlorate is a widely occurring contaminant, which can competitively inhibit iodide uptake and thus thyroid hormone production. The health effects of chronic low dose perchlorate exposure are largely unknown. In a community-based study, we compared thyroid function and disease in women with differing likelihoods of prior and current perchlorate exposure. Residential blocks were randomly selected from areas: (1) with potential perchlorate exposure via drinking water; (2) with potential exposure to environmental contaminants; and (3) neighboring but without such exposures. Eligibility included having lived in the area for $\geq$6 months and aged 20–50 years during 1988–1996 (during documented drinking water well contamination). We interviewed 814 women and collected blood samples (assayed for thyroid stimulating hormone and free thyroxine) from 431 interviewed women. Daily urine samples were assayed for perchlorate and iodide for 178 premenopausal women with blood samples. We performed multivariable regression analyses comparing thyroid function and disease by residential area and by urinary perchlorate dose adjusted for urinary iodide levels. Residential location and current perchlorate dose were not associated with thyroid function or disease. No persistent effect of perchlorate on thyroid function or disease was found several years after contaminated wells were capped.

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INTRODUCTION

Perchlorate is used in a variety of products (e.g., road flares, explosives, pyrotechnics and solid rocket propellant)[1] and is found in a variety of foods, including milk and milk products, spinach and carrots (http://www.fda.gov/Food/FoodSafety/FoodContaminantsAdulteration/ChemicalContaminants/Perchlorate/ucm077685.htm, accessed September 2011). It is an inorganic anion that competitively inhibits iodide uptake,[2–4] thus inhibiting thyroid hormone (thyroxine, T4 and triiodothyronine, T3) production at mg/day doses.[5] The pituitary gland, in response to this inhibition, increases the release of thyroid stimulating hormone (TSH).[6] Potassium perchlorate originally was used (until the 1960s) to treat primary hyperthyroidism, a condition causing overproduction of T3 and T4. However, the effects of perchlorate on healthy individuals, particularly those with chronic low dose exposure, are largely unknown. Two small studies of workers exposed by breathing ammonium perchlorate showed no effects on thyroid, liver, bone marrow or kidney function.[7,8] Oral administration of 0.5 mg perchlorate or 3.0 mg potassium perchlorate daily to 13 healthy volunteers or up to 0.5 mg/kg/day given to 37 healthy adults also was not associated with TSH or T4.[3,9] A Chilean study of 184 pregnant women with high perchlorate exposure (median 35 μg/l, $>$99th percentile in the US NHANES study)[10] found no relation with thyroid function.[11] The National Research Council[12] estimated that chronic exposure to $>$0.4 mg perchlorate/kg/day (equivalent to 14 μg/l in a 70-kg person drinking 2 l/day) may cause hypothyroidism in an iodine-replete population. However, a study by the Centers for Disease Control and Prevention (CDC) showed that women with low urinary iodide levels ($<$100 μg/l) may be more susceptible to the hypothyroid effects of perchlorate.[13]

In Sacramento, a community residing near a National Priority List site[14] became contaminated from hazardous waste disposal by burial, open burning, discharge into unlined ponds and injection into underground wells.[15] The prevailing winds near the site are largely to the east and north. The closest residence was about 500 feet from the site. Soil contaminants included volatile organic compounds, perchlorate and metals (arsenic, beryllium, cadmium, chromium, cobalt, copper, lead, nickel and zinc). Contaminants in the groundwater plume included volatile organic compounds (trichloroethylene (TCE), chloroform, perchloroethylene, toluene, methylene chloride, n-nitrosodimethyl-amine and perchlorate).[16] In 1982, the TCE-contaminated groundwater was extracted, treated and re-injected back into the aquifer, continuing through 1996 when the re-injected treated water was found to contain perchlorate. Perchlorate was detected in five off-site public drinking water wells containing between 93 and 250 ppb perchlorate.[17] Perchlorate exposure via drinking water may have begun in 1988 and continued until contaminated wells were capped in 1997. During this time no tap water perchlorate measurements were taken in the affected areas.

We hypothesized that perchlorate exposure might be related to adverse thyroid effects in residents living adjacent to this site. We conducted an epidemiological study of women to compare thyroid function and disease and current perchlorate exposure in

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women who were likely and those who were unlikely to have had prior elevated perchlorate exposure by:

A comparing current serum (TSH and free thyroxine (fT4)) levels in three study areas;
B comparing proportions with self-reported underactive thyroid, overactive thyroid or thyroid medication use by study area;
C comparing current urinary perchlorate levels in three study areas; and
D examining the relation of urinary perchlorate levels to serum TSH and fT4 as well as to self-reported thyroid disorders.

MATERIALS AND METHODS

Sampling Design and Sample Selection

From 2001 to 2007, we conducted a community-based, cross-sectional study with historical ascertainment of health outcomes. Residential blocks were randomly selected from three areas, selected based on potential historical exposure or non-exposure to perchlorate, those: (1) near the perchlorate-contaminated drinking water plume (Area A); (2) with potential exposure to airborne contaminants following open burning of waste materials (Area B); and (3) in similar neighboring areas without such known potential exposures (Area C).

We randomly sampled blocks from a commercial list and enumerated households in each of the three study areas. The list was constructed from a national database whose sources were: telephone directories, auto registration, real estate records and multi-verified proprietary sources (credit card files, subscriptions, credit reports from TRW Inc., driver licenses, voter registration and census data). The database contained 90 percent of households in the country (96 million) and 170 million individuals. We supplemented our listings of households using the Haines Criss + Cross Directory database for each randomly selected block. Households on randomly selected blocks were screened for eligibility until 275 women from distinct households participated in each of the three areas. Eligibility included having lived at the residence for $\geq$6 months and being aged 20–50 years during 1988–1996 (during documented contamination of drinking water wells). Households selected received a letter asking when was best to contact them. If they did not respond after three mailings, we telephoned them to ascertain willingness to be screened and the best time for eligibility screening by telephone.

We identified 5262 households and screened 1473 women (28%). Of the remaining 3789 households: 579 (11.0%) women refused screening; 706 (13.4%) women had moved out of the area; 162 (3.1%) women did not speak English; 212 (4.0%) households did not include a woman; 227 women (4.3%) were not reachable; and for 1903 women (36.2%) a phone number could not be determined. Of the 1473 screened women, 1132 (76.8%) were eligible; multiple calls on different days and different times of day were made to schedule eligible women for interview, and 814 (71.9%) were interviewed.

Procedures

The UC Davis Human Subjects Review Committee approved the study protocol. All participants provided signed, written informed consent before interview. Blood samples were collected from the first 431 women interviewed (equally distributed across the three study areas, $n = 134$–148 per area provided blood samples). Thyroid function assays were completed in all 431 blood samples collected, but blood collection was suspended for the remaining 377 participants because of lack of difference by area in thyroid function measures. Blood was permitted to clot, centrifuged and stored at -20°C.

Premenopausal participants completed a daily diary, recording menstruation and symptoms, and collected one 5 ml sample of first morning urine each day for two menstrual cycles, beginning with the onset of the first menstrual period following the interview. Urine samples were stored in their freezers until they completed collection; then, samples were transported by study staff in coolers on dry ice to UC Davis where they were stored at -20°C until thawed for pooling. Previous studies indicate that perchlorate is stable in frozen urine.[10]

The CDC analyzed pooled urine samples from one cycle of the first 178 women who were still menstruating, corresponding to the 431 women who also had blood samples assayed for thyroid function. Over 95% of these urine samples were collected during 2001–2004. For each woman, we pooled the daily samples into three menstrual cycle phases: early phase = days 1–10; mid-cycle = days 11–17; and late phase = days 18–28. Creatinine levels for each of the pools were determined in the UC Davis endocrine laboratory.

Laboratory Assays

The TSH assay was a very sensitive, two-site sandwich immunoassay using direct chemiluminometrics with constant amounts of a monoclonal mouse anti-TSH antibody labeled with acridinium ester and a polyclonal sheep anti-TSH antibody, covalently coupled to paramagnetic particles. The fT4 assay was a competitive immunoassay using direct chemiluminescence. FT4 competed with acridinium ester-labeled T4 for a limited amount of polyclonal rabbit anti-T4 antibody, which was covalently coupled to paramagnetic particles. Both TSH and fT4 were run on the automated Centaur instrument at the UC Davis Medical Center.

Pooled urine samples were shipped on dry ice to the CDC and analyzed for perchlorate, thiocyanate, iodide and nitrate using ion chromatography tandem mass spectrometry.[13,18] Perchlorate levels in frozen urine samples do not change with extended storage time.[13] Urine was spiked with isotopically-labeled internal standard, diluted 1:1 with deionized water and analyzed using ion chromatography-electrospray ionization-tandem mass spectrometry. The four analytes were quantified by the peak area ratio of analyte to internal standard. The limits of detection and coefficients of variation were 0.05 μg/l and 4.2% for perchlorate, 0.33 μg/l and 4.9% for iodide, 5.0 μg/l and 2.2% for thiocyanate, 500 μg/l and 1.4% for nitrate. Results for all assays met the quality control and quality assurance criteria for accuracy and precision of the Division of Laboratory Sciences, National Center for Environmental Health, CDC.[19] Average perchlorate dose was computed from measured urinary perchlorate and estimated 24-h urinary creatinine/day, using the Cockcroft–Gault[20] equation as modified by Mage:[21]

$$\text{g creatinine/day} = 10^{-6} * 164 * (140 - \text{age (years)}) * \text{weight (kg)}^{1.5} * \text{height (cm)}^{0.5}$$

and

$$\text{Perchlorate dose} = \mu\text{g perchlorate/g urinary creatinine} * \text{g creatinine/day} * 1/\text{weight (kg)}$$

Outcome Variables

Our primary outcomes in the full sample of 814 women were self-reported. We asked "Has a doctor ever told you that you have an overactive thyroid" or "underactive thyroid". We also asked: "In the last month have you taken thyroid pills?" and "Have you ever taken thyroid medicines (e.g., synthroid)?" Our primary outcomes in the subsample of women who provided blood samples were fT4 and TSH levels (normal ranges 0.8–1.8 ng/dl and 0.35–5.5 mIU/l, respectively).

Independent Variables

We included: study area A, B or C; duration of residence in the area and at current residence; water source for drinking and cooking; and eating vegetables grown at home in the study area. For women who provided urine samples, computed average perchlorate dose and urinary iodide, thiocyanate and nitrate levels were also independent variables.

Covariates

We included standard demographic questions (age, race/ethnicity, difficulty paying for basics (including food, housing, medical care and heat), health insurance, education, annual household income, employment, marital status),[22] smoking,[23,24] physical activity,[25,26] body mass index (BMI) (computed from self-reported weight in kg/(height in m)^2), family history of thyroid disease and self-assessed health status).[22]

Data Analyses

We compared the characteristics of the study population across the three study areas using ANOVA to test for differences in continuous variables and χ^2-tests for categorical variables. For the entire sample of 814 women, we computed unadjusted odds ratios (ORs) for each thyroid disease outcome separately for areas A and B compared with area C, for sources of drinking and cooking water and whether women

Table 1. Characteristics of participants.

Characteristic[a]	*Total sample (N = 814)*		*Sample w/blood (N = 431)*		*Sample w/urine (N = 181)*		P-*value*[b]
	n	%	n	%	n	%	
Study area							*0.37*
A	296	36.36	148	34.34	60	33.15	0.24
B	264	32.43	148	34.34	58	32.04	0.28
C	254	31.2	135	31.32	63	34.81	0.59
Age (years)							*<0.01*
<30	33	4.05	23	5.34	6	3.31	0.86
30–39.99	135	16.58[c,d]	101	23.43[c]	34	18.78[d]	<0.01
40–49.99	418	51.35[c,d]	266	61.72[c,e]	131	72.38[d,e]	<0.01
50–59.99	228	28.01[c,d]	41	9.51[c]	10	5.52[d]	<0.01
Race/ethnicity							*0.74*
Black/African-American/African	24	2.95	13	3.02	4	2.22	0.68
Caucasian (non-Hispanic, White)	701	86.22	368	85.58	155	86.11	0.57
Hispanic	39	4.80	28	6.51	10	5.56	0.17
Asian/Pacific Islander	25	3.08	11	2.56	5	2.78	0.77
Other/mixed	24	2.95	10	2.33	6	3.33	0.78
Education							*0.02*
≤High school/GED	102	12.55	60	13.95	24	13.33	0.68
Some college/vocational school	313	38.50	184	42.79	74	41.11	0.05
College grad	240	29.52	122	28.37	56	31.11	0.84
≥Some graduate/professional school	158	19.44[c,d]	64	14.88[c]	26	14.45[d]	<0.01
Marital status							*<0.01*
Single/never married	137	16.85[c]	97	22.56[c]	27	15.00	<0.01
Married/partnered	572	70.36	282	65.58	135	75.00	0.13
Separated/divorced/widowed	104	12.79	51	11.86	18	10.00	0.39
Annual household income							*0.01*
<$35 K	79	10.23	51	12.53	13	7.47	0.03
$35–$75 K	275	35.62[c]	161	39.56	73	41.95[c]	0.04
>$75 K	418	54.15	195	47.91	88	50.57	0.03
Missing	42		24		7		
Difficulty paying for basics							*0.36*
Very hard	41	5.06	30	6.99	9	5.03	0.26
Somewhat hard	186	22.96	100	23.31	39	21.79	0.41
Not very hard	583	71.98	299	69.70	131	73.18	0.53
Currently employed							*0.27*
No	174	21.38	90	20.88	37	20.44	0.27
Yes	640	78.62	341	79.12	144	79.56	0.27
Health insurance							*0.01*
Private	746	91.76[c]	378	87.91	160	88.4[c]	<0.01
Public	46	5.66[c]	38	8.84	14	7.73[c]	<0.01
None	21	2.58	14	3.26	7	3.87	0.48
Self-rated health							*0.60*
Excellent	204	25.15	115	26.81	47	26.11	0.70
Very good	353	43.53	176	41.03	85	47.22	0.43
Good	194	23.92	104	24.24	38	21.11	0.76
Fair + poor	60	7.40	34	7.93	10	5.55	0.22
Smoking							*0.03*
Never	523	64.25	264	61.25	119	65.75	0.13
Former	191	23.46	102	23.67	47	25.97	0.73
Current	100	12.29[c]	65	15.08[c]	15	8.29	0.01
Physical activity							*0.10*
Much less	81	9.96[c]	52	12.09[c]	14	7.73	<0.01
Somewhat less	147	18.08	87	20.23	33	18.23	0.55
The same	216	26.57	108	25.12	50	27.62	0.58
Somewhat more	238	29.27	116	26.98	55	30.39	0.28
Much more	131	16.11	67	15.58	29	16.02	0.96

Table 1. (Continued).

Characteristic[a]	*Total sample (N = 814)*		*Sample w/blood (N = 431)*		*Sample w/urine (N = 181)*		P-*value*[b]
	n	%	n	%	n	%	
BMI (kg/m^2), mean (SD)	808	26.99 (6.54)	430	27.04 (6.76)	180	26.35 (5.48)	0.50
Menopausal status							*<0.01*
Menopausal due to hysterectomy	82	10.076[c]	31	7.19[c]	—	—	<0.01
Postmenopausal	118	14.50[c]	34	7.89[c]	—	—	<0.01
Late perimenopausal	23	2.83[c]	11	2.55[d]	1	0.55[c,d]	<0.01
Early perimenopausal	181	22.24[c]	92	21.35[d]	62	34.25[c,d]	<0.01
Premenopausal	288	35.38[c,d]	195	45.24[c,e]	117	64.64[d,e]	<0.01
Pregnant	7	0.86	1	0.23	—	—	0.32
Medically induced menopause	17	2.09	8	1.86	—	—	0.62
Missing (or undetermined)	98	12.04[c]	59	13.69[d]	1	0.55[c,d]	<0.01
Drinking water source							*0.60*
Private well	4	0.49	1	0.23	1	0.55	0.60
Municipal water supply	400	49.20	217	50.35	87	48.07	0.31
Bottled only	212	26.08	117	27.15	52	28.73	0.36
Other	196	24.11	96	22.27	41	22.65	0.35
Cooking water source							*0.11*
Private well	6	0.74	1	0.23	1	0.55	0.20
Municipal water supply	655	80.67[c]	363	84.22[c]	145	80.11	0.02
Bottled only	26	3.20	11	2.55	4	2.21	0.52
Other	124	15.27	55	12.76	30	16.57	0.09
Grow/eat own vegetables							*0.07*
No	516	63.94[c]	291	67.67[c,d]	103	57.54[d]	0.01
Yes	290	35.94	139	32.33	76	42.46	0.03
Residence duration at current address (years), mean (SD)	814	13.14 (7.91)[c,d]	431	10.7 (6.56)[c]	181	11.48 (6.38)[d]	<0.01
Residence duration in area (years)							*<0.01*
Entire life	36	4.43	25	5.81	8	4.42	0.36
20+	290	35.67[c]	135	31.4[c]	62	34.25	<0.01
11–20	329	40.47	161	37.44	69	38.12	0.23
5–10	132	16.24[c,d]	91	21.16[c]	38	20.99[d]	<0.01
3–4	14	1.72	9	2.09	1	0.55	0.45
≤2	12	1.48	9	2.09	3	1.66	0.14

[a]Sums may not equal total due to missing values, not shown if <1% of total. [b]*P*-values from ANOVA for continuous variables and chi-square tests for categorical variables. *P*-value compares across three data sets: [c,d,e]indicate results that differ significantly.

grew and ate their own vegetables. We performed ANOVAs for comparing mean values of TSH and fT4, and Fisher's exact test for comparing proportions of women with TSH or fT4 values outside the normal range for the subsample of 431 women with blood samples across the three study areas.

We assessed potential confounding variables for their relation to the independent and dependent variables using likelihood ratio tests and retained in multivariable modeling those which modified the ORs or regression coefficients by >10%.[27,28] We modeled each categorical outcome in multiple logistic regressions comparing separately areas A and B to area C, sources of drinking and cooking water and whether women grew and ate their own vegetables. We modeled mean TSH and fT4 and the odds of either of these being outside the normal range in multiple linear regression and logistic regression models, respectively, comparing study areas.

For the 178 women who had pooled urine and blood samples, we compared the three study areas for sociodemographic and health characteristics and for mean, geometric mean and median values of urinary perchlorate, iodide, thiocyanate and nitrate. We identified confounding variables using the criteria noted above and computed multivariable regression models to examine differences among the three areas, adjusted for these variables. We performed multiple regression analyses for the relation of urinary perchlorate levels and dose to TSH and fT4 adjusting for iodide <100 *vs* ≥100 μg/l. As none of the four urinary analytes differed significantly across the three phases of the menstrual cycle, mean, geometric mean and median values for each urinary analyte across the three phases were computed and used in all analyses.

RESULTS

Demographic and Health Characteristics

The total sample and the subsample of women with blood samples did not differ significantly by residence location, race/ethnicity, difficulty paying for basics, current employment, self-rated health, physical activity, BMI, drinking or cooking water source (Table 1). As expected, the total sample differed from the subsample of women who provided urine samples because of the eligibility criterion (still menstruating) for the latter, who were significantly younger, less likely to be postmenopausal and significantly less likely to be current smokers and more likely to grow and eat their own vegetables. Small statistically significant differences were also observed with the total sample having slightly higher educational levels, annual household income, more private health insurance and longer residence at the current address.

Thyroid Disease and Function by Area

No significant differences were observed in any of the demographic, lifestyle and health factors by respondent's residential area (data not shown). Further, no significant differences were observed by residential area in personal or family history of thyroid disease, nor in mean or median TSH or fT4 or in the proportion

Table 2. Thyroid function and disease by study area.

(a) Thyroid disease

	Total (N = *814*)		*Area*						P-*value*[a]
			A		B		C		
	n	%	n	%	n	%	n	%	
Family history of thyroid disease									*0.26*
No	533	66.71	200	67.57	179	67.8	154	60.63	0.15
Yes	266	33.29	93	31.42	79	29.92	94	37.01	0.19
Ever hyperthyroidism									*0.76*
No	787	96.92	284	95.95	257	97.35	246	96.85	0.67
Yes	25	3.08	11	3.72	6	2.27	8	3.15	0.58
Current hyperthyroidism									*0.21*
No	808	99.26	296	100	261	98.86	251	98.82	0.21
Yes	6	0.74	0	0	3	1.14	3	1.18	0.21
Ever hypothyroidism									*0.59*
No	729	89.56	269	90.88	233	88.26	227	89.37	0.59
Yes	85	10.44	27	9.12	31	11.74	27	10.63	0.59
Current hypothyroidism									*0.76*
No	751	92.26	275	92.91	241	91.29	235	92.52	0.76
Yes	63	7.74	21	7.09	23	8.71	19	7.48	0.76
Ever thyroid medications									*0.35*
No	752	92.38	274	92.57	248	93.94	230	90.55	0.35
Yes	62	7.62	22	7.43	16	6.06	24	9.45	0.35
Current thyroid medications									*0.64*
No	739	90.9	272	91.89	236	89.39	231	90.94	0.59
Yes	74	9.1	24	8.11	27	10.23	23	9.06	0.68

(b) Thyroid stimulating hormone (TSH) and free thyroxine (fT4)[b]

	Total with blood (n = *392*)	*Area*			P-*value*
		A (n = *134*)	*B* (n = *148*)	*C* (n = *135*)	
TSH (mIU/l)[c]					
Mean (SD)	2.01 (1.42)	1.97 (1.34)	2.06 (1.55)	1.98 (1.36)	0.856
Median	1.72	1.68	1.785	1.75	0.976
n (%) above normal (>5.5)	16 (4.08)	7 (5.22)	6 (4.51)	3 (2.40)	0.494
n (%) TSH>3.5	36 (9.18)	11 (8.21)	14 (10.53)	11 (8.8)	0.794
fT4 (ng/dl)[d]					
Mean (SD)	1.11 (0.15)	1.19 (0.16)	1.11 (0.15)	1.11 (0.15)	0.892
Median	1.11	1.11	1.1	1.12	0.962
n (%) below normal (<0.8)	5 (1.28)	1 (0.75)	2 (1.5)	2 (1.6)	0.796
Clinical hypothyroidism					
n (%) TSH >5.5 mIU/l and fT4 <0.8 ng/dl	1 (0.26)	0 (0)	1 (0.75)	0	NA
Subclinical hypothyroidism					
n (%) TSH >3.5 mIU/l and fT4 0.8–1.8 ng/dl	35 (8.93)	11 (8.21)	13 (9.77)	11 (8.8)	0.90

[a]*P*-value (by exact test) compares three study areas; Note: no pair-wise comparisons between a pair of study areas significantly differed. [b]Excluding current users of thyroid medication. [c]None below normal (<0.35). [d]None above normal (>1.8).

with values of these measures outside the normal range in pair-wise comparisons between any two study areas (Table 2). No significant differences were observed in the total sample in history of thyroid disease by drinking or cooking water sources (except for a significant association of using municipal water for cooking with ever use of thyroid medication, with wide confidence intervals due to small numbers reporting these outcomes) (Table 3). These findings also held in the subsamples of women who provided blood or urine samples, although the sample sizes were much smaller (data not shown).

In bivariate analyses, BMI, age, race/ethnicity, annual household income, having health insurance, financial strain, employment and menopausal status were related to some thyroid disease outcomes. Thus, we included these covariates in multiple logistic

Table 3. Unadjusted odd ratios (ORs) for thyroid outcomes ($n = 814$).

Outcome	Drinking water source				Cooking water source				Grow vegetables	
	Municipal water supply		Other		Municipal water supply		Other			
	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI	OR[b]	95% CI
Ever hyperthyroidism	0.52	(0.17, 1.61)	0.51	(0.15, 1.78)	1.01	(0.13, 7.73)	1.34	(0.14, 13.38)	1.42	(0.63, 3.16)
Current hyperthyroidism	0.67	(0.051, 8.64)	2.0	(0.09, 44.35)	NA[c]	NA[c]	NA[c]	NA[c]	3.67	(0.51, 26.2)
Ever hypothyroidism	1.03	(0.59, 1.80)	0.72	(0.38, 1.30)	2.06	(0.82, 5.19)	1.99	(0.69, 5.72)	0.86	(0.53, 1.41)
Current hypothyroidism	1.20	(0.33, 4.44)	1.56	(0.36, 6.80)	0.74	(0.079, 6.89)	1.0	(0.072, 13.9)	1.37	(0.43, 4.37)
Ever thyroid medication	0.76	(0.39, 1.49)	0.64	(0.30, 1.34)	3.20	(1.25, 8.20)	2.17	(0.74, 6.33)	0.93	(0.54, 1.61)
Current thyroid medication	0.71	(0.38, 1.33)	0.63	(0.31, 1.26)	1.01	(0.30, 3.40)	1.19	(0.31, 4.60)	0.94	(0.57, 1.57)

Abbreviations: CI, confidence of interval; NA, not applicable.
[a]"Bottled + private" is reference. [b]Response = no is used as the reference. [c]NA = cell count <5, so OR is not available.

regression models for the outcomes to which they were related in comparing these outcomes by residential area, sources of drinking or cooking water or whether women grew and ate their own vegetables. Multivariable models indicated that residential area was not significantly related to any thyroid outcomes in the total sample (Table 4) or in the subsamples of women who provided blood or urine samples (data not shown).

Thyroid Function and Disease by Perchlorate Dose

No significant differences were observed among study areas in mean, geometric mean or median computed perchlorate, thiocyanate, iodide or nitrate levels (data not shown). Perchlorate doses ranged from 0.034 to 0.42 μg/kg/day (mean = 0.12 μg/kg/day), and thus did not in any participant exceed the Environmental Protection Agency reference dose of 0.7 μg/kg/day. Perchlorate dose was not significantly related to TSH or fT4 levels (data not shown), and mean and median levels of TSH and fT4 did not differ significantly across tertiles of computed perchlorate dose (Table 5).

Finally, in the subsample of women who provided urine samples, multiple logistic regression models revealed no significant relation of computed perchlorate dose to ever or current hypothyroidism, adjusting for the covariates related to these outcomes, including urinary iodide levels (Table 6). Similar results were found for thiocyanate and nitrates (data not shown).

DISCUSSION

We found no association of residential area that previously had drinking water wells contaminated with perchlorate with current thyroid function or thyroid disease, after controlling for confounding. Thus, no long-term adverse thyroid effects persisted from prior contamination several years after the wells were capped. We also found no association of computed perchlorate dose with current thyroid function or thyroid disease, indicating that currently consumed perchlorate levels appeared to have no adverse relation to thyroid health.

The effects of perchlorate on thyroid function were recently reviewed.[29] The first essential step in thyroid hormone synthesis involves iodide uptake by the sodium/iodide symporter,[30] a membrane protein on the follicular cell adjacent to the capillaries supplying blood to the thyroid.[31] Perchlorate is environmentally stable and a widespread contaminant in drinking and irrigation water and in food.[10,32] It competitively inhibits iodide uptake,[6,33] potentially depressing thyroid hormone production. The serum half-life of perchlorate in humans is about 7.5 h,[34] and a dose of 5.2 μg/kg/day reduces the thyroid's iodide uptake.[3] Only those in the much higher 0.5 mg/kg/day dosage group showed reduced iodide uptake and TSH, the latter being unexpected.[34] Greer et al.[3] noted, if iodine intake is of adequate frequency and magnitude, intermittent periods of low intake may not affect thyroid hormone production.

Our results are consistent with the finding of a small human experiment of no effect of 10 mg perchlorate/day consumed in spring water for 14 days on TSH or serum thyroid hormones.[5] Two occupational studies of workers exposed to ammonium perchlorate dust, mostly through ingestion or inhalation, also showed no adverse effect on thyroid function at single-shift doses of airborne perchlorate averaging 36 μg/kg[35] or up to 34 mg/day[8] and no long-term thyroid effects.[7] Thus, our results agreed with findings examining higher exposures than in our study. Further, our findings also agree with those from a cohort study comparing Clark County, Nevada in which drinking water contained perchlorate up to 16 μg/l, to Washoe County, whose water did not contain perchlorate, and to the rest of the state and found no difference in thyroid disease prevalence rates.[36]

All of our study participants had measurable levels of urinary perchlorate, albeit at doses less than the reference dose. These results are consistent with urinary perchlorate levels and computed perchlorate doses from the NHANES,[10] although the average dose was somewhat higher (0.12 μg/kg/day) in our study compared with that in the NHANES (0.061 μg/kg/day). Urinary perchlorate levels have been associated with serum TSH and total T4 in US women but not men;[13] this association was stronger in women with urinary iodide <100 μg/l and even stronger among women who smoked,[37] likely because cigarette smokers have higher levels of the iodide uptake inhibitor, thiocyanate. We found no such associations, but the small number in our study with low iodide levels or who smoked did not provide sufficient statistical power to detect such differences as significant.

Strengths and Limitations

Our study had a number of significant strengths, including a large, community-based sample and laboratory assessment of thyroid function and of computed perchlorate dose and iodide levels. We also collected data on many sociodemographic, health and lifestyle variables, enabling us to control for confounding by these variables. Further, our laboratory assessments of thyroid function and computed perchlorate dose were masked so that: the laboratory staff assessing thyroid function were unaware of the residential location or perchlorate dose of participants; and the staff assessing urinary perchlorate and iodide levels were unaware of the participants' residential location, thyroid function or disease status.

The present study also had a number of limitations. First, the design was cross-sectional, which limited the ability to assess the temporal relation between exposures and thyroid function and disease outcomes, and we had no measures of historical perchlorate levels in the tap water or in the participants. A cross-sectional study in which these historical outcomes were ascertained was a reasonable compromise, although residents

Table 4. Multiple logistic models: odds ratios (OR) and 95% confidence intervals (CI) for thyroid diseases, total sample ($N = 814$).

	Overall P	*OR*	*95% CI*	P-*value*
(a) *Ever hyperthyroidism*				
BMI (kg/m^2)	0.19	1.04	(0.98, 1.11)	0.19
Age (years)	0.08	1.06	(0.99, 1.13)	0.08
Race/ethnicity (*vs* Caucasian)	0.85			
Black/African-American		<0.01	(<0.01, 999.99)	0.98
Hispanic		2.027	(0.39, 10.54)	0.4
Asian/other		0.78	(0.10. 6.18)	0.81
Annual household income (*vs* >$75K)	0.68			
<$35K		0.64	(0.13, 3.30)	0.6
$35–$75K		1.26	(0.48, 3.33)	0.640
City (*vs* Area C)	0.81			
Area A		1.05	(0.37, 2.97)	0.92
Area B		0.73	(0.22, 2.39)	0.6
Health insurance (*vs* none)	<0.01			
Private		0.04	(0.01, 0.16)	<0.01
Public		0.06	(0.01, 0.56)	0.01
(b) *Current hyperthyroidism*				
BMI (kg/m^2)	0.61	4.71	(<0.012, >999.99)	0.61
Age (years)	0.61	0.21	(<0.01, 89.39)	0.61
Race/ethnicity (*vs* Caucasians)	0.99			
Black/African-American		NA[a]	NA[a]	
Hispanic		>999.99	(<0.01, >999.99)	0.99
Asian/other		>999.99	(<0.01, >999.99)	0.94
Annual household income (*vs* >$75K)	0.90			
<$35K		<0.01	(<0.01, >999.99)	0.92
$35–$75K		>999.99	(<0.01, >999.99)	0.66
City (compared with Area C)	0.86			
Area A		<0.001	(<0.01, >999.99)	0.66
Area B		<0.001	(<0.01, >999.99)	0.88
Grow/eat own vegetable (yes *vs* no)	0.74	>999.99	(<0.01, >999.99)	0.74
(c) *Ever hypothyroidism*				
BMI (kg/m^2)	<0.01	1.07	(1.03, 1.11)	<0.01
Age (years)	0.06	10.04	(0.99, 1.08)	0.06
Race/ethnicity (*vs* Caucasians)	0.59			
Black/African-American		1.52	(0.43, 5.33)	0.51
Hispanic		0.31	(0.04, 2.31)	0.25
Asian/other		1.22	(0.45, 3.32)	0.7
Annual household income (*vs* >$75K)	0.47			
<$35K		1.25	(0.57, 2.77)	0.58
$35–$75K		0.78	(0.44, 1.38)	0.39
City (*vs* Area C)	0.26			
Area A		0.59	(0.31, 1.11)	0.1
Area B		0.82	(0.45, 1.51)	0.53
Currently employed (yes *vs* no)	0.68	0.88	(0.49, 1.60)	0.68
Menopausal status (*vs* premenopausal)	0.26			
Hysterectomy		0.68	(0.23, 2.04)	0.49
Postmenopausal		1.43	(0.61, 3.35)	0.41
Late/early perimenopausal		1.33	(0.66, 2.68)	0.43
Undetermined/HT use		2.14	(0.97, 4.69)	0.06
Medically induced menopause		2.45	(0.61, 9.88)	0.21
(d) *Current hypothyroidism*				
BMI (kg/m^2)	0.09	1.09	(0.99, 1.21)	0.09
Age (years)	0.92	1.00	(0.94, 1.06)	0.92

Table 4. (Continued).

	Overall P	*OR*	*95% CI*	P-*value*
Race/ethnicity (*vs* Caucasians)	0.38			
Black/African-American		0.14	(0.01, 3.16)	0.22
Hispanic		>999.99	(<0.01, >999.99)	0.99
Asian/other		0.22	(0.03, 1.94)	0.17
Annual household income (*vs* >$75K)	0.95			
<$35K		1.46	(0.08, 25.62)	0.80
$35–$75K		1.20	(0.26, 5.57)	0.82
City (*vs* Area C)	0.81			
Area A		1.67	(0.33, 8.47)	0.54
Area B		1.49	(0.30, 7.56)	0.63
(e) *Ever thyroid medication*				
BMI (kg/m^2)	0.04	1.05	(1.00, 1.09)	0.04
Age (years)	<0.01	1.10	(1.05, 1.15)	<0.01
Race/ethnicity (*vs* Caucasians)	0.47			
Black/African-American		0.50	(0.06, 4.26)	0.52
Hispanic		1.38	(0.37, 5.14)	0.63
Asian/other		0.24	(0.03, 1.88)	0.17
Annual household income (*vs* >$75K)	0.71			
<$35K		0.64	(0.20, 2.06)	0.45
$35–$75K		1.00	(0.50, 2.01)	1.00
City (*vs* Area C)	0.08			
Area A		0.71	(0.36, 1.42)	0.33
Area B		0.39	(0.18, 0.88)	0.02
Difficulty paying for basics (*vs* not hard)	0.03			
Very hard		4.12	(1.44, 11.81)	0.01
Somewhat hard		1.32	(0.60, 2.92)	0.49
(f) *Current thyroid medication*				
BMI (kg/m^2)	<0.01	1.08	(1.04, 1.12)	<0.01
Age (years	0.05	1.04	(1.00, 1.08)	0.05
Race/ethnicity (*vs* Caucasians)	0.37			
Black/African-American		0.56	(0.11, 2.91)	0.49
Hispanic		0.36	(0.05, 2.74)	0.32
Asian/other		0.26	(0.03, 1.92)	0.18
Annual household income (*vs* >$75K)	0.57			
<$35K		1.52	(0.66, 3.49)	0.32
$35–$75K		1.00	(0.54, 1.85)	1.00
City (*vs* Area C)	0.81			
Area A		0.82	(0.42, 1.60)	0.56
Area B		0.83	(0.42, 1.65)	0.60

Abbreviations: BMI, body mass index; NA, not applicable.
[a]NA means no participants had hyperthyroidism so that OR could not be calculated.

who had moved away and who might have had different outcomes from those who remained were not included; the magnitude and direction of any resulting bias cannot be reliably estimated. Second, although we achieved a good participation rate (72%) among eligible women, this participation rate cannot eliminate the possibility of selection and participation biases; thus, those who were more likely to be concerned about their health or environmental exposures might have been more likely to participate, and those who might have been more adversely affected might have moved away and not been contacted. Third, some of our outcome assessments depended on participants' self-report of a physician ever having told them that they had underactive or overactive thyroid, which may have resulted in misclassification of these outcomes. Such misclassification is unlikely to have been differential with regard to perchlorate exposure and thus was likely to attenuate any relationship to such exposure. Fourth, the use of location of residence as a surrogate for exposure in some of our analyses was likely to result in misclassification of exposure, which was probably non-differential with regard to the outcomes assessed, and thus could have attenuated effect estimates. The individual measures of urinary perchlorate levels, however, should have significantly reduced misclassification, although the sample size was smaller, resulting in reduced statistical power compared with the analyses using residential location. Fifth, even with the study's large sample size (ranging from 135 to 296 per group, depending on the exposure measure used), the numbers of women who reported ever or currently having thyroid diseases or using thyroid medication or who had TSH elevated above the normal range were too small (5–10% of women per group) and the differences in these proportions between areas were also too small to provide sufficient statistical power, that is, at least 80% power, with a

Table 5. Thyroid stimulating hormone (TSH) and free thyroxine (fT4) levels by tertiles of perchlorate dose[a], urine subsample ($n = 128$).

	Perchlorate dose tertile			P-*value*[b]
	Lowest (<0.086 μg/kg/day) (n = *44*)	*Middle (0.086–0.128 μg/kg/day)* (n = *43*)	*Highest (>0.128 μg/kg/day)* (n = *41*)	
TSH (mIU/ml)				
Mean (SD)	2.31 (1.92)	2.02 (1.55)	1.87 (1.26)	0.434
Median	1.84	1.52	1.78	0.478
Minimum, maximum	0.19, 10.6	0.51, 8.13	0.43, 6.50	
n (%) above normal (>5.5)	3 (6.98%)	2 (4.65%)	2 (4.88%)	1
fT4 (ng/dl)				
Mean (SD)	1.11 (0.17)	1.11 (0.17)	1.13 (0.13)	0.825
Median	1.1	1.08	1.13	0.488
Minimum, maximum	0.8, 1.63	0.73, 1.46	0.87, 1.56	

[a]Restricted to subsample of women with both blood and urine and not currently using thyroid medications. [b]*P*-value comparing among dose tertiles.

Table 6. Multiple logistic models: odds ratios (ORs) and 95% confidence intervals (CI) for ever or current hypothyroidism related to perchlorate dose, adjusted for urinary iodide level, $n = 176$.

	Overall P	*OR*	*95% CI*	P-*value*
Perchlorate dose	0.51	0.67	(0.20, 2.23)	0.51
Iodide (<100 *vs* ≥100[a])	0.94	1.10	(0.11, 10.75)	0.94
Age	0.38	0.95	(0.85, 1.06)	0.38
Race/ethnicity (*vs* Caucasians)	0.94			
Black/African-American		0.43	(0.03, 5.71)	0.52
Hispanic		>999.99	(<0.01, >999.99)	0.97
Asian/other		>999.99	(<0.01, >999.99)	0.96
Annual household income (*vs* >$75K)	0.69			
<$35K		>999.99	(<0.01, >999.99)	0.96
$35–$75K		0.60	(0.19, 1.91)	0.39
Health insurance (*vs* none)	0.97			
Private		<0.01	(<0.01, >999.99)	0.98
Public		<0.01	(<0.01, >999.99)	0.98

[a]Excluding women reporting using thyroid medication for an unspecified reason.

two-sided $\alpha = 0.05$, to detect a relation of thyroid disease or dysfunction to residential area or to computed perchlorate dose in the subset of women who provided urine samples. We do note that the prevalence of history of hyperthyroidism or hypothyroidism and current hypothyroidism in our study was similar to published figures.[38,39] Finally, thyroid disease was ascertained solely by self-report and was not validated, possibly resulting in some misclassification of thyroid disease outcomes, although elevated TSH or low fT4 were objectively determined by serum measures, and perchlorate exposure was objectively determined from urine samples, reducing misclassification in these determinations in the subset of women who had them.

CONCLUSIONS

We found no persistent, long-term relation of prior perchlorate drinking water contamination on thyroid disease or function several years after the contaminated drinking water wells were capped. We also found no relation of current computed perchlorate dose to current thyroid hormone levels or to thyroid disease. Thus, currently consumed levels of perchlorate, which were below the reference dose, did not appear to be adversely related to thyroid health in our study sample of largely iodine replete and largely non-smoking women, although caution must be used in drawing these conclusions, given the small number of women in our study sample with abnormal thyroid function, disease or medication use.

ABBREVIATIONS

cm, centimeters; fT4, free thyroxine; kg, kilograms; mIU/l, milli-international units/liter; ng/dl, nanograms/deciliter; NHANES, National Health and Nutrition Examination Survey; T3, triiodothyronine; TCE, trichloroethylene; TSH, thyroid stimulating hormone

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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