

Thyroid Health Status of Ammonium Perchlorate Workers: A Cross-Sectional Occupational Health Study

Steven H. Lamm, MD
Lewis E. Braverman, MD
Feng Xiao Li, MD, DrPH
Kent Richman, PhD
Sam Pino, BSc
Gregory Howearth, BSc

Since pharmaceutical exposures to perchlorate are known to suppress thyroid function in patients with hyperthyroidism, a study of employees at a perchlorate manufacturing plant was conducted to assess whether occupational exposure to perchlorate suppresses thyroid function. Exposure to perchlorate was assessed by measurement of ambient air concentrations of total and respirable perchlorate particles, and systemic absorption was assessed by measurement of urinary perchlorate excretion. Airborne exposures ranged from 0.004 to 167 mg total particulate perchlorate per day. Urinary perchlorate measurements demonstrated that exposure to the airborne particulate perchlorate resulted in systemic absorption. Workers were grouped into four exposure categories with mean absorbed perchlorate dosages of 1, 4, 11 and 34 mg perchlorate per day. Thyroid function was assessed by measurement of serum thyroid-stimulating hormone, free thyroxine index, thyroxine, triiodothyronine, thyroid hormone binding ratio, thyroid peroxidase antibodies, and by clinical examination. No differences in thyroid-function parameters were found between the four groups of workers across approximately three orders of magnitude of exposure and of dose. Thus human thyroid function was not affected by these levels of absorbed perchlorate. In addition, no clinical evidence of thyroid abnormalities was found in any exposure group. The blood-cell counts were normal in all groups, indicating no evidence of hematotoxicity in this exposure range. The absence of evidence of an effect on thyroid function or blood cells from occupational airborne perchlorate exposure at a mean absorption of 34 mg/day demonstrates a no-observed-adverse-effect-level (NOAEL) that can assist in the evaluation of human health risks from environmental perchlorate contamination.

This occupational health study was conducted in July 1998 at the only US industrial site currently manufacturing ammonium perchlorate (the Cedar City, Utah, site of American Pacific Corporation). The purpose was to assess the health status—specifically, the thyroid function—of workers with long-term (months to years) exposure to perchlorate. This study included measures of perchlorate particulates to determine exposure; measures of urinary perchlorate to determine the magnitude of systemic absorption from perchlorate particulates; and measures of thyroid function to determine whether (and if so, to what degree) thyroid function was affected by the perchlorate absorption. Although this study was primarily designed to develop a health assessment of occupationally exposed perchlorate workers, the information gathered may also be useful in assessing health risks to persons who are environmentally exposed to perchlorate.

For over 50 years, perchlorates have been used industrially as oxidizers in propellants and explosives because their salts have strong oxidizing potential. Ammonium perchlorate is used as the oxidizer in solid propellant for rockets and missiles, such as the boosters for the space shuttle and the Titan rocket, as well as for fireworks. Other commonly used perchlorate salts include sodium perchlorate, which is used as an oxidizer in slurry explosives manufacturing, and potassium perchlor-

From Consultants in Epidemiology and Occupational Health, Inc. (CEOH, Inc.), Washington, DC (Dr Lamm, Dr Li); the Department of Medicine, Brigham & Women's Hospital, Boston, Mass. (Dr Braverman, Mr Pino); and American Pacific Corporation, Cedar City, Utah (Dr Richman, Mr Howearth).

Address correspondence to: Steven H. Lamm, MD, Consultants in Epidemiology and Occupational Health, Inc., 2428 Wisconsin Ave. NW, Washington, DC 20007.

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ate, which is used in road flares and in air bag inflation systems. Perchlorate salts are highly soluble in water. Perchlorate ions have been detected in ground and surface waters near sites where perchlorates are used or manufactured or where perchlorate-containing fertilizers are used. The perchlorate salts fully ionize, and the perchlorate ion (ClO_4^-) persists for several decades in surface and ground waters. Recent improvements in the laboratory method for detecting perchlorate in drinking-water supplies have lowered the limit of detection from 400 parts per billion (ppb) to 4 ppb. Subsequent surveys of water supplies in California have detected perchlorate in a number of wells, the sources of which have been traced back to various sites of industrial perchlorate use, and in a major water supply (the Colorado River, downstream from Lake Mead), the source of which has been traced back to an area of perchlorate manufacture in Nevada. Some of the well measurements in California have exceeded 18 ppb, and the water measurements from the Colorado River have ranged from 5 to 8 ppb. The potential health risks from short-term and long-term consumption of such levels of perchlorate in drinking-water supplies are currently under assessment by the US Environmental Protection Agency.

Although thyroid function is dependent upon an adequate dietary intake of iodine (100 to 200 $\mu\text{g}/\text{day}$) as a substrate for hormone synthesis, the thyroid readily compensates for a modest decrease in iodine intake by enlarging and actively transporting a larger fraction of the circulating iodine. An Austrian study showed that euthyroid subjects ($n = 2308$) had normal levels of the thyroid hormone thyroxine (T_4) despite having mildly low iodine intakes (as indicated by urinary excretion of $<100 \mu\text{g I}$ per gram creatinine).¹

Studies in humans and rodents demonstrate that the primary effect of perchlorate is to block the uptake

of iodine by the thyroid gland, thus potentially decreasing the production of the thyroid hormones T_4 and triiodothyronine (T_3). Perchlorate (as potassium perchlorate) has been used medically since the late 1950s to treat hyperthyroidism, and its effects on the thyroid have been well studied.² It is a competitive inhibitor of the sodium/iodide symporter of the thyroid follicular cell, which actively transports iodine from the blood into the thyroid. It does not appear to have an important effect on thyroid-hormone synthesis. Perchlorate is the most effective drug for blocking the thyroidal uptake of iodine. It is excreted unmetabolized, with approximately 95% recovery in urine over 72 hours.³ Eichler³ reported that within 6 to 8 hours, the urine contained 50% of a 1- or 2-gram oral dose given to an adult male. Similarly, Durand⁴ reported that within 5 to 9 hours, the urine contained 50% of a 0.8-gram oral dose given to an adult male.

In 1952, Stanbury and Wyngaarden⁵ demonstrated the effectiveness of perchlorate in treating hyperthyroidism due to Graves' disease at dose levels of 200 mg potassium perchlorate three times daily. Subsequently, treatment doses were increased to 1200 mg per day to accelerate the induction of normal thyroid function. After case reports of fatal aplastic anemia or agranulocytosis in patients treated with perchlorate at doses of 600 to 1600 mg/day for extended periods, the use of perchlorate for treating Graves' disease markedly decreased. More recently, Wenzel and Lente⁶ treated hyperthyroid patients with Graves' disease with perchlorate at doses of 900 mg or below daily for 1 year with excellent results and no serious side effects. Perchlorate is now used to treat patients who have iodine-induced thyrotoxicosis (eg, amiodarone-associated thyrotoxicosis [AAT]). Amiodarone, a potent drug used to treat cardiac tachyarrhythmias, contains nearly 40% iodine. AAT patients treated for 1 month or longer

with perchlorate at doses up to 1000 mg perchlorate per day had no evidence of agranulocytosis or aplastic anemia.⁷⁻¹⁰

Few studies have been conducted on the effect of perchlorate on healthy human subjects. In a 1974 study, Burgi et al¹¹ showed in five healthy volunteers that 600 mg/day for 1 week increased non-thyroxine iodine release by 65% and suggested that it might completely block iodide uptake by the thyroid. In a 1992 study, Brabant et al¹² were unable to induce a state of iodine depletion in five healthy male volunteers by oral administration of 900 mg potassium perchlorate per day for 4 weeks. Brabant et al were reported to have subsequently observed mild goiters without an increase in thyroid-stimulating hormone (TSH) levels in a 5-week-long repeat of that study. These are the only studies that indicate effect levels from perchlorate exposure in healthy humans.

The occupational health study presented here focuses on thyroid health status and was conducted in an ammonium perchlorate manufacturing plant. The manufacturing process at this plant begins with the electrolysis of brine (sodium chloride in water) to form sodium chlorate (NaClO_3) first and then sodium perchlorate (NaClO_4). Ammonium chloride (NH_4Cl) is formed from ammonia (NH_3) and hydrochloric acid (HCl). The sodium perchlorate is reacted with the ammonium chloride to form ammonium perchlorate (NH_4ClO_4) and salt (NaCl). The solution is cooled, and the ammonium perchlorate crystals are dried and blended to specifications.

Study Design

This was a cross-sectional study of two similar worker populations from the same industrial complex: ammonium perchlorate production workers and sodium azide production workers. The latter served as a comparison group. The purpose was to assess perchlorate exposure and thyroid function in both groups. The two

production plants are in close proximity, and the workers share locker facilities, storage areas, training and administrative areas, etc, but not production areas.

Perchlorate exposure was measured using full-shift breathing zone air sampling for total perchlorate particles and respirable perchlorate particles. Urinary perchlorate concentration was assessed at the beginning and end of the 12-hour shift in which the particulate exposure was measured. Particle-size-selective sampling was conducted to obtain the mass median aerodynamic diameter of the particles.

Thyroid function was assessed by measuring serum TSH, T_4 , and T_3 concentrations, the thyroid hormone binding ratio (THBR), and the free T_4 index (FTI). Thyroid peroxidase (TPO) antibody concentrations were measured to identify workers with underlying Hashimoto's thyroiditis. If the occupational exposure to perchlorate had been suppressing the thyroid by blocking iodine uptake, the expected observation would have been that the TSH levels would have increased.

Urinary iodine concentrations were obtained to determine whether workers had adequate iodine intake. Blood samples for complete blood counts (CBCs) and serum samples for a chemistry panel were also obtained. Physical examinations and medical histories with careful thyroid evaluation were performed on all subjects.

Materials and Methods

Study Population

The perchlorate production plant is located in the industrial facility of the American Pacific Corporation in Iron County, Utah, west of Cedar City. The facility, which began production in 1989, employs approximately 190 workers in four major divisions. The 39 employees assigned to direct perchlorate production and the 21 employees assigned to azide production were eligible to

be study participants. Employees assigned to administrative, engineering, maintenance, and supervisory positions were not eligible for study participation. Fifty-eight of the 60 employees eligible for participation did participate. Two of the eligible perchlorate workers were not at the plant at the time of the study because of vacation or military duty and did not participate. The production employees work 12-hour shifts (on 3 days; off 3 days), with rotation from days to night approximately monthly. The employee populations from both plants are similar in that they are drawn from the same population base, have the same management procedures and policies, work similar rotating shifts, and have participated in prior medical monitoring programs at the facility.

All participants were instructed as to the nature of the study, and informed consent was obtained. The study protocol and consent forms were approved by the Georgetown University School of Medicine institutional review board. Pre-shift and post-shift urine samples were obtained from all participants, and post-shift blood samples were obtained from all but one participant, who declined to give a blood sample. Air-sampling equipment was used throughout the shift for determining both total and respirable perchlorate particle exposure. Participants completed a medical questionnaire and underwent a physical examination conducted by a local physician's assistant and a thyroid examination conducted by a thyroid specialist (L.E.B.). Examiners were not aware of participant's study groups. Laboratory samples were prepared with participant code numbers to keep the laboratory personnel blinded as to each participant's study group. The personnel and director of each laboratory maintained quality control and assurance procedures.

Perchlorate Exposure Groups

The job assignments of the perchlorate production workers were

classified into three categories of presumptive exposure (low, medium, and high), based on the visible dust generated. The categories of low, medium, and high were used as follows to classify workers:

- A—Low: employees handling only solutions or slurries of perchlorates. This includes the electrolysis through crystallization processes.
- B—Medium: employees handling limited quantities of dry perchlorates, resulting in only minor visible-dust exposure. This includes the initial drying process.
- C—High: employees handling large quantities of dry perchlorates, resulting in significant visible-dust exposure. This includes the blending and packaging operations.

Urine Samples

Pre- and post-shift urine samples were collected from all participants to measure urinary perchlorate, iodine, and creatinine levels. Urine samples were frozen after collection and thawed prior to analysis. Urinary creatinine and iodine measurements were performed in the Iodine Research Laboratory at the Brigham & Women's Hospital (Boston, MA), using the Jaffee alkaline picrate method for creatinine and the Sandell-Koltoff reaction for iodine (modification of Benotti et al¹³). Urinary perchlorate measurements were performed by Dr Kent Richman at the American Pacific Corporation laboratory. The method (Richman et al¹⁴; available on request) is capable of measuring urinary perchlorate concentrations of 0.5 parts per million (ppm) or greater.

Blood Samples

Post-shift blood samples were collected. CBCs were performed at the clinical laboratories of the Valley View Medical Center, Cedar City, Utah. The CBC included absolute counts of red blood cells, white blood cells, and platelets; absolute and relative counts of lymphocytes, neutrophils, monocytes, eosinophils,

and basophils; and hemoglobin, hematocrit, and red cell parameters (mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration).

Serum Samples for Thyroid-Function Studies

Thyroid-function studies on post-shift serum samples were performed in the Endocrine-Hypertension Research Laboratory of the Brigham & Women's Hospital. Thyroid-function studies were carried out in duplicate, in the same assay, and in random order. The following tests and their methods were performed (normal values for the laboratory are indicated in parentheses): TSH (0.45 to 4.5 $\mu\text{U/mL}$) was measured by chemiluminescence (Beckman Access, Chaska, MN); T_4 (5 to 11 $\mu\text{g/dL}$) and THBR (0.85 to 1.10) by radioimmunoassay (Diagnostic Products Corp., Los Angeles, CA); T_3 (87 to 178 ng/dL) by radioimmunoassay (Beckman Access); and TPO (<20 IU/mL) by enzyme-linked immunosorbent assay (American Laboratory Products Co, Windham, NH). The FTI index is the product of the T_4 concentration and the THBR. The results reported for each subject are the mean of the duplicate values for each test.

Serum Sample for Blood Chemistry Panel

Post-shift serum samples obtained from the participants were collected for analysis of a chemistry panel by Quest Diagnostics (Cambridge, MA). The chemistry panel included measurements of serum levels of calcium, phosphate, glucose, blood urea nitrogen, creatinine, uric acid, cholesterol, total protein, albumin, alkaline phosphatase, lactic dehydrogenase, aspartate aminotransferase, and total bilirubin.

Air Sampling

Full-shift air sampling for total (<40 μm) and respirable (<10 μm)

breathing-zone particles was carried out under the direction of David Houck, CIH (Kerr-McGee Corporation, Oklahoma City, OK). For measurement of total particulates, 5- μm polyvinyl chloride filters in 37-mm, three-piece, closed-face cassettes were used, with a sampling rate of approximately 2 liters per minute and a sampling duration of 10 to 11 hours. For measurement of respirable particulates, SKC aluminum cyclones (SKC Corporation, Eighty Four, PA) were used with 5- μm polyvinyl chloride filters in 37-mm cassettes, at a flow rate of 1.9 liters per minute.

Montgomery-Watson Laboratories (Pasadena, CA) analyzed the cassettes for perchlorate. Cassette samples were dissolved in a 10-mL aliquot of 30 mM sodium hydroxide, and perchlorate concentration was measured using the California Department of Health Services analytic method for perchlorate in drinking-water samples.

Size-selective sampling of airborne dust was performed during a production period with a Marple 8-stage Cascade Impactor (Andersen Instruments Inc., Smyrna, GA) in the blender building at a height of 5 feet above the floor in the area where the perchlorate C group worked. Particle size distributions were determined at the following eight cut points: 21.3 μm , 14.8 μm , 9.8 μm , 6.0 μm , 3.5 μm , 1.55 μm , 0.93 μm , and 0.52 μm . Dust particles in the range of 0.1 to 10 μm are generally considered to be "respirable," because they may enter and be retained by the deep regions of the lung. Total particle mass was also determined since the highly soluble perchlorate particle may be readily absorbed after deposition into the nasal passages or upper respiratory tract. Inhalable particles, which may also precipitate in the upper respiratory tract areas, were not separately measured. The mass mean aerodynamic diameter of the particles was calculated.

Urinary Perchlorate Excretion

To determine the time course of urinary perchlorate excretion, two workers were monitored for 6 days, with urine samples submitted every 12 hours. These employees worked in the high-exposure area during the first 12 hours of each of the first 3 days; in the next 3 days, they were assigned to the administrative building rather than to the production area. Thus the observation period includes three exposure periods followed by 3½ days of observation with no known exposure. The urinary perchlorate levels during the 3 unexposed days provide an indication of perchlorate elimination rates under the conditions of exposure experienced by these two workers.

Methods of Statistical Analysis

Statistical analysis of data was conducted using the Stata package for the personal computer (Stata Corporation, College Station, TX). A *t* test was applied to mean differences in all continuous-exposure, outcome, and demographic variables. Descriptive statistics for exposure and outcome variables were calculated and presented as arithmetic and/or geometric means and standard deviations, medians, ranges (minimum and maximum), and interquartile ranges (25th percentile and 75th percentile). For categorical variables, a chi-square statistic was used. Two-tailed *P* values were calculated for each comparison. The absence of a statistically significant difference was inferred if the two-tailed *P* value was not less than 0.05. For outcome data, pairwise *t* tests were performed between the comparison group and each of the exposed groups. A non-parametric *z* test for trend across ordered groups was conducted.¹⁵

Results

Population Description

A total of 58 employees participated in this occupational health study: 37 from the ammonium perchlorate production plant (35 males

TABLE 1
Descriptive Statistics of Respirable and Total Airborne Perchlorate Levels (mg/day), by Plant and Exposure Groups*

Groups	n	Ar-Mean	Ar-SD	Geo-Mean	Geo-SD	Min	P ₂₅	Median	P ₇₅	Max
Respirable, mg/day										
Azide	6	0.021	0.014	0.017	1.925	0.009	0.010	0.014	0.038	0.039
Perchlorate A	11	0.091	0.095	0.057	3.019	0.006	0.040	0.067	0.083	0.331
Perchlorate B	7	0.601	0.671	0.255	5.196	0.031	0.031	0.374	1.522	1.575
Perchlorate C	14	8.591	9.386	5.414	2.740	0.957	2.643	5.040	10.160	35.852
Total, mg/day										
Azide	4	0.014	0.012	0.011	2.482	0.004	0.006	0.012	0.023	0.030
Perchlorate A	6	0.337	0.187	0.288	1.921	0.107	0.168	0.330	0.487	0.602
Perchlorate B	2	6.567	7.139	4.200	—	1.519	1.519	6.567	11.615	11.615
Perchlorate C	12	59.378	53.605	28.674	5.101	1.036	11.772	44.890	103.749	166.996

* Ar-Mean, arithmetic mean (average); Ar-SD, standard deviation of the arithmetic mean; Geo-Mean, geometric mean (logarithmic mean); Geo-SD, standard deviation of the geometric mean; Min, minimum value; P₂₅, 25th percentile value; Median, 50th percentile value; P₇₅, 75th percentile value; Max, maximum value.

and two females) and 21 from the sodium azide production plant (19 males and two females), ranging in age from 20 to 56 years. The mean age of the ammonium perchlorate workers was 30 years, compared with 35 years in the azide workers. Forty percent of the ammonium perchlorate production workers and 50% of azide production workers had been employed for more than 5 years.

Medical Examination and Questionnaire Findings

No differences were found between the azide workers and the perchlorate workers or among the three perchlorate worker groups in the findings from their medical examinations or their responses on the medical questionnaire. Mean heights and weights were similar. The groups did not differ in their clinical findings (blood pressure, pulse rate, examination of body systems) from the medical examination. According to their answers on the medical questionnaire, the groups did not differ in alcohol or tobacco use, in medication use, in frequencies of family history of major systemic diseases (diabetes, hypertension, rheumatoid arthritis, thyroid disease, or cancer), or in reported medical problems.

Thyroid disease was identified in two workers. One worker in the low perchlorate exposure group (A) had

been previously diagnosed with Graves' disease. His disease was diagnosed 9 years prior to this employment and had been treated with radioactive iodine. During this study, he was found to be hypothyroid and undermedicated. Previously undiagnosed thyroid disease was found in only one worker, a worker in the medium perchlorate exposure group (B), who was found in this examination to have an autoimmune condition of the thyroid, euthyroid Hashimoto's thyroiditis. Other than the first worker, no worker reported a history of either thyroid disease or thyroid medication.

Airborne Exposure

The 37 perchlorate participants included 14 employees in the nominally low perchlorate exposure jobs, eight employees in the nominally medium perchlorate exposure jobs, and 15 employees in the nominally high perchlorate exposure jobs. All 37 perchlorate participants wore air samplers. Thirty-two wore respirable-particle samplers, and 21 wore total-particle samplers. Seven of the 21 azide participants wore air samplers. Six wore respirable particle samplers, and four wore total particle samplers. Table 1 lists the respirable and total airborne perchlorate exposures (mg/day) of the workers, stratified by exposure group. This was calculated from the laboratory report

of the amount of perchlorate in the sampling cassettes, the air-sampling rate (approximately 2 liters/minute) and duration (approximately 10 hours), and the assumption of an inhalation rate of 1.2 cubic meters per hour. Data are presented as the arithmetic and geometric means and standard deviations, along with the range, median, and distribution by quartiles. Data in this table demonstrate that airborne perchlorate particle levels are greater in the dusty parts of the perchlorate plant than in the azide plant and that both respirable-particle and total-particle perchlorate inhalation progressively increase with visible-dust level in the perchlorate plant exposure groups. The exposures of the high-exposure perchlorate group are clearly discernible from the other worker groups, being three orders of magnitude greater than those of the azide workers. The minimal exposures of the azide workers may come from contamination from the shared non-production facilities or contamination of their worksite. Data in this table also show that patterns of distribution for respirable and total particles across the exposure groups are similar. Individual measures of respirable- and total-particle perchlorate were highly correlated with a statistically significant correlation coefficient ($r = 0.82$; $P \ll 0.01$), based on 18 paired samples. Respirable particle

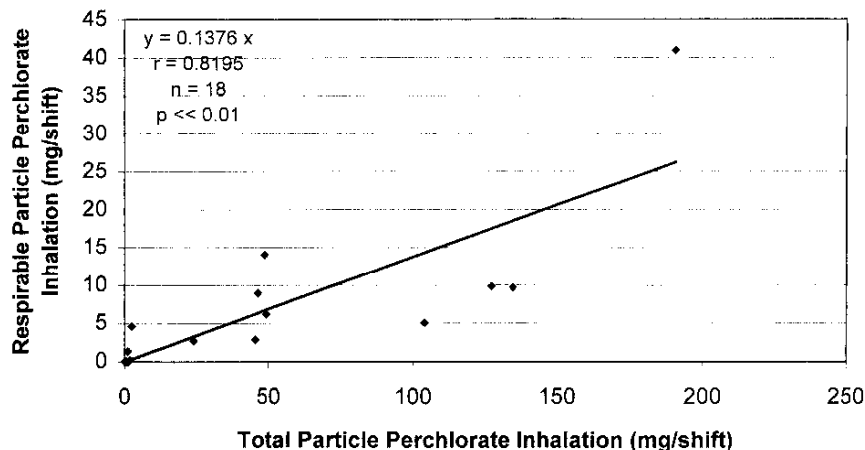


Fig. 1. Perchlorate particle inhalation: comparison of paired respirable-particle and total-particle measures.

inhalation accounted for 14% of the total-particle inhalation rate (Fig. 1).

Particle size-selective sampling conducted in the blender operation (perchlorate exposure group C area) yielded a mass median aerodynamic diameter of the particles of 7.4 μm , with a geometric standard deviation of 3.8.

Urinary Perchlorate Levels

Table 2 presents mean urine perchlorate levels (mg/g creatinine) for the azide plant workers and for each perchlorate exposure group. The data are presented for the pre-shift urine sample, for the post-shift urine sample, and for a post-shift (adjusted) measure. The data are presented as the arithmetic mean and its standard deviation, the range, the median, and the quartiles.

The pre-shift urine was collected before the work shift, and the post-shift urine was collected at the end of the work shift. The post-shift urine perchlorate measurement reflects two components: (a) the excretion due to the residual perchlorate that was present in the body at the time of the pre-shift urine perchlorate measure, and (b) the incremental increase in urinary perchlorate due to the excretion of the perchlorate that was inhaled (or ingested) during the work shift.

The post-shift (adjusted) measure is defined to represent the post-shift

urinary perchlorate component that reflects perchlorate inhaled during the shift. The body burden represented by the pre-shift urinary perchlorate measure is estimated by pharmacokinetic modeling (assuming first-order kinetics and an 8-hour excretory half-life) to be reduced by 65% after 12 hours. The post-shift (adjusted) urinary perchlorate estimate was obtained by subtracting 35% of the pre-shift urinary perchlorate measure from the post-shift urinary perchlorate measure as an exposure estimate adjustment. This first-order model follows the equation $E_i - E_o e^{-kt} = D(1 - e^{-kt})$, where E is the excretion rate of perchlorate at time (i) and time (o) and D is the dose rate from exposure. For a half-life of 8 hours and at time 12 hours, e^{-kt} equals 0.354. The post-shift (adjusted) measure is $E_i - 0.354 E_o$.

Table 2 demonstrates that workers in the three perchlorate exposure groups have progressively increasing levels of urinary perchlorate. Symmetry about the means and the similarities between the mean and the median in each strata suggest that log transformation of the data is unnecessary.

Absorbed Dose

The absorbed dose can be calculated for each shift directly from the

data listed in Table 2. From the model equation above, with 12-hour work shifts and an 8-hour half-life, the excreted dose (D) follows the equation $D = k [E_i - 0.354 E_o] / 0.646$. The term $[E_i - 0.354 E_o]$ is the post-shift (adjusted) level in mg perchlorate per gram creatinine. The human adult creatinine excretion rate of 1 mg/minute links perchlorate excretion rates in terms of creatinine to rates in terms of time. The percent absorbed that is excreted into the urine is assumed to be 95%, as shown by Eichler.³ The exposure rate was measured as a time-weighted average exposure. The excreted dose is, then, 12 hours \times 60 minutes per hour \times 0.001 g/mg \times 1 mg creatinine/minute \times [post-shift adjusted]/0.646 and the absorbed dose is the excreted dose/0.95, which is expressed in mg/shift. This represents a reasonable estimate of perchlorate absorption over a 12-hour shift (mg/shift) and is calculated independently of the exposure estimates.

Thyroid Function Status

Table 3 presents the mean thyroid-function tests for the azide production workers and for each of the perchlorate exposure groups, along with the standard deviations, ranges, medians, and distribution by quartiles. There were no differences in thyroid-function tests between workers in the azide and perchlorate plants or between the azide workers and any of the three perchlorate exposure groups. Extreme outlier values due to specific thyroid diseases were excluded from the analysis, as indicated in Table 3. Pairwise *t* tests were performed between the azide group and each of the three perchlorate exposure groups. As listed in Table 3, none of the comparisons were statistically significant at $\alpha < 0.05$ level. A nonparametric *z* test for trend across the ordered groups for each of the six thyroid function tests, using the method developed by Cuzick,¹⁵ found no statistically significant trend (although the trend for

TABLE 2

Descriptive Statistics of Creatinine-Adjusted Urine Perchlorate Levels (mg/gm), by Plant and Exposure and Adsorbed Dose (mg/shift)*

Groups	n	Mean	SD	Min	P ₂₅	Median	P ₇₅	Max
Pre-shift								
Azide	21	1.31	1.55	0.23	0.39	0.84	1.36	6.37
Perchlorate A	14	2.05	2.42	0.42	0.59	1.09	1.50	8.02
Perchlorate B	8	5.98	5.70	0.64	1.12	4.87	9.91	15.41
Perchlorate C	14	11.30	9.93	0.53	1.09	14.89	17.61	30.22
Post-shift								
Azide	21	1.19	1.16	0.16	0.52	0.81	1.52	4.97
Perchlorate A	14	4.07	2.15	0.46	2.38	3.53	5.71	8.24
Perchlorate B	8	11.27	7.59	3.63	4.93	9.79	16.45	24.22
Perchlorate C	15	32.22	13.14	11.16	27.81	33.09	38.89	64.38
Post-shift, adjusted								
Azide	21	0.75	1.00	-0.85	0.14	0.53	0.78	3.62
Perchlorate A	14	3.39	2.29	0.32	1.69	2.87	5.02	8.04
Perchlorate B	8	9.28	7.41	2.67	3.13	7.16	13.32	23.98
Perchlorate C	14	28.66	12.38	10.80	21.04	28.43	33.70	58.51
Adsorbed dosage, mg/shift								
Azide	21	0.88	1.17	-1.00	0.16	0.62	0.92	4.25
Perchlorate A	14	3.98	2.69	0.38	1.98	3.37	5.89	9.43
Perchlorate B	8	10.89	8.69	3.13	3.67	8.40	15.63	28.13
Perchlorate C	14	33.62	14.52	12.67	24.68	33.35	39.54	68.65

* Groups: azide, comparison; A, low perchlorate; B, medium perchlorate; C, high perchlorate.

TFI was of borderline significance but in a direction opposite that which was pharmacologically predicted).

Categorical data analyses also were conducted with normal values for T_4 , T_3 , FTI, and THBR being defined as values at or above the normal lower limit for the laboratory and with normal values of TSH and anti-TPO being defined as values at or below the normal upper limit for the laboratory. There were no significant differences across the exposure groups, between the two plants, or in comparison to the laboratory range of normal. In no case did the proportion of abnormal values for the perchlorate workers exceed that for the azide workers. There were no suggestive trends, either statistically or clinically, for any thyroid-function test. Furthermore, no differences in the thyroid-function tests were observed in the perchlorate plant workers as a result of their inhaled and excreted perchlorate levels. These findings show that thyroid function is not altered in workers exposed at the perchlorate levels found in this plant.

Thyroid Examinations

Clinical examination of the thyroid glands of all participants revealed no significant thyroid abnormalities in any group. The thyroid glands did not differ in size, texture, or shape between the two groups or across the perchlorate exposure groups. No goiters were detected in any of the workers. A small nodule was detected in a worker in a low perchlorate exposure job. Secondary signs of hypothyroidism and of hyperthyroidism were sought by the thyroid examiner (L.E.B.) and were not observed. There was no evidence of bradycardia, tachycardia, or tremor. Examination of the skin, eyes, and extremities did not reveal signs of thyroid disease.

Urinary Iodine Excretion

The pre-shift urinary iodine values of the azide and perchlorate workers met international standards, with 95% or more having a urinary iodine level of 50 $\mu\text{g/L}$ or greater. More than 90% of each group had pre-shift urinary iodine levels greater than 100 $\mu\text{g/L}$. These data indicate the ab-

sence of iodine deficiency in these groups of workers.

The pre-shift urinary iodine values did not differ between the perchlorate workers (mean, 318 $\mu\text{g/L}$; standard deviation, 164 $\mu\text{g/L}$) and the azide workers (mean, 344 $\mu\text{g/L}$; standard deviation, 180 $\mu\text{g/L}$). Analysis was limited to the 49 specimens with pre-shift urinary iodine values less than 800 $\mu\text{g/L}$, because greater values suggest contamination from extraneous sources. Additionally, the urinary iodine values adjusted for creatinine excretion did not differ between the perchlorate workers (mean, 192 $\mu\text{g/g}$; standard deviation, 132 $\mu\text{g/g}$) and the azide workers (mean, 211 $\mu\text{g/g}$; standard deviation, 120 $\mu\text{g/g}$).

Pre-shift and post-shift urinary iodine levels were compared. There was no evidence of increased iodine excretion post-shift, compared with pre-shift, for either the azide or perchlorate workers, based on those 44 paired urine samples with values that did not suggest contamination (ie, <800 $\mu\text{g/L}$). The pre-shift and post-shift urine iodine levels did not differ

TABLE 3
Descriptive Statistics of Thyroid-Function Parameters, by Plant and Exposure Groups*

Groups	n	Mean	SD	Min	P ₂₅	Median	P ₇₅	Max	P Value [†]
T₄ (5 to 11 µg/dL)[‡]									
Azide	21	6.73	1.479	4.60	5.40	6.80	7.40	9.90	—
Perchlorate A	13	7.13	1.583	4.00	6.40	6.90	7.80	10.60	0.46
Perchlorate B	8	7.34	1.115	5.40	6.70	7.50	8.00	8.90	0.31
Perchlorate C	15	7.03	1.301	4.40	6.00	7.30	8.10	8.60	0.54
T₃ (87 to 178 ng/dL)									
Azide	21	142.52	17.543	113.00	129.00	143.00	156.00	169.00	—
Perchlorate A	13	148.38	25.178	96.00	145.00	159.00	166.00	174.00	0.43
Perchlorate B	8	152.13	23.234	120.00	134.00	148.00	176.00	181.00	0.24
Perchlorate C	15	152.13	20.368	108.00	141.00	150.00	165.00	192.00	0.14
TSH (0.45 to 4.5 µU/mL)									
Azide	21	3.14	1.870	0.67	2.00	2.80	4.10	8.40	—
Perchlorate A	12	2.68	1.143	1.20	1.70	2.50	3.75	4.50 [§]	0.45
Perchlorate B	8	2.41	1.271	0.75	1.45	2.15	3.50	4.30	0.32
Perchlorate C	15	3.33	2.338	0.65	1.50	2.80	4.20	8.20	0.80
FTI (5.0 to 11.0)									
Azide	21	6.05	1.248	4.40	5.30	6.00	6.70	9.60	—
Perchlorate A	13	6.33	1.435	3.20	5.80	6.40	6.90	9.40	0.55
Perchlorate B	8	6.56	0.847	5.10	6.25	6.50	6.90	8.10	0.29
Perchlorate C	15	6.56	1.022	4.40	5.60	6.90	7.20	8.20	0.20
THBR (0.85 to 1.10)									
Azide	21	0.90	0.071	0.80	0.84	0.91	0.95	1.08	—
Perchlorate A	13	0.89	0.064	0.79	0.83	0.89	0.93	0.99	0.47
Perchlorate B	8	0.90	0.069	0.79	0.85	0.90	0.96	0.99	0.81
Perchlorate C	15	0.94	0.094	0.78	0.87	0.95	1.01	1.09	0.19
Anti-TPO (<20 IU/mL)									
Azide	21	9.28	11.274	5.00	5.00	5.00	6.30	53.20	—
Perchlorate A	13	9.26	10.611	5.00	5.00	5.00	5.00	42.70	0.98
Perchlorate B	8	11.38	9.524	5.00	5.00	5.00	18.20	29.60	0.65
Perchlorate C	14	8.63	6.797	5.00	5.00	5.00	9.50	29.60	0.85

* T₄, thyroxine; T₃, triiodothyronine; TSH, thyroid-stimulating hormone; FTI, free T₄ index; THBR, thyroid hormone binding ratio; Anti-TPO, thyroid peroxidase antibodies.

[†] All *t* tests were performed assuming equal variances based on Bartlett's test for equal variances (at an α level of 0.05).

[‡] Values in parentheses represent the laboratory's normal range for the assay.

[§] One extreme outlier (TSH, 38 µU/mL) was excluded. This worker was diagnosed with Graves' disease 9 years before employment and was insufficiently treated for his hypothyroidism, which developed after ¹³¹I therapy.

^{||} One extreme outlier (anti-TPO, 709 IU/mL) was excluded. This worker has euthyroid Hashimoto's thyroiditis.

for the perchlorate workers (pre-shift: mean, 294 µg/L, standard deviation, 150 µg/L; post-shift: mean, 297 µg/L, standard deviation, 175 µg/L) or for the azide workers (pre-shift: mean, 350 µg/L, standard deviation, 189 µg/L; post-shift: mean, 325 µg/L, standard deviation, 202 µg/L).

Complete Blood Counts

The blood counts showed no difference between the perchlorate workers and the azide workers, either directly or when the perchlorate workers were stratified by exposure groups. The mean of the red cell counts, white blood cell counts (including lymphocytes, neutrophils,

monocytes, etc) and platelet counts revealed no significant differences across the exposure groups (Table 4). The proportion of workers with red cell counts, white blood cell counts, or platelet counts below the normal laboratory ranges were similar in all groups. No significant trends were observed in the blood-cell data whether examined as continuous variables or as categorical variables. Neither the mean nor the proportion abnormal were found to be significantly different for the azide group or any of the perchlorate groups when each of the 18 cellular parameters were examined. There was no evidence for aplastic anemia, agranulocytosis, or neutropenia. No sug-

gestion of hematotoxicity was seen among the perchlorate-exposed workers or the azide-exposed workers.

Other Clinical Parameters

Serum chemical profiles were conducted on workers. The clinical chemistry results showed no evidence of either renal or hepatic toxicity. The frequency of elevated serum cholesterol levels was greater than 5% among the azide and the perchlorate workers. The serum phosphate level was the only chemical variable that showed significantly higher values among the perchlorate workers than among the azide workers. No explanation for this finding is apparent. There were no differences

TABLE 4
Descriptive Statistics of Blood Cell Counts, by Plants and Exposure Groups

Groups	n	Mean	SD	Min	P ₂₅	Med	P ₇₅	Max	P Value
Red blood cells (4.40 to 5.80 × 10 ³ /nL) [†]									
Azide	21	5.16	0.333	4.30	5.00	5.20	5.40	5.73	—
Perchlorate A	14	5.06	0.500	4.10	4.90	5.22	5.30	5.70	0.48
Perchlorate B	8	5.11	0.233	4.74	4.95	5.14	5.28	5.40	0.66
Perchlorate C	15	5.37	0.367	4.40	5.00	5.50	5.60	5.76	0.10
White blood cells (3.6 to 10.6 cells/nL) [†]									
Azide	21	8.62	5.608	4.90	6.81	7.60	8.30	32.60	—
Perchlorate A	14	7.67	1.380	5.50	7.20	7.30	7.90	11.00	0.47*
Perchlorate B	8	7.83	2.631	4.40	5.45	7.85	9.90	11.80	0.61*
Perchlorate C	15	7.99	1.554	5.90	6.50	7.80	8.70	11.80	0.63*
Neutrophils (1.8 to 8.0 cells/nL) [†]									
Azide	21	4.96	5.222	1.80	3.50	3.60	4.40	27.50	—
Perchlorate A	14	4.41	0.796	2.90	4.10	4.65	4.80	5.50	0.64*
Perchlorate B	8	4.20	1.546	2.30	3.00	4.40	4.65	7.20	0.55*
Perchlorate C	15	4.30	1.214	2.20	3.40	4.30	4.70	7.70	0.58*
Lymphocytes (1.2 to 3.4 cells/nL) [†]									
Azide	21	2.66	0.691	1.30	2.30	2.60	2.80	4.10	—
Perchlorate A	14	2.39	0.659	1.60	1.90	2.20	2.60	4.30	0.27
Perchlorate B	8	2.83	1.516	1.50	1.75	2.30	3.55	5.90	0.77*
Perchlorate C	15	2.81	0.822	1.10	2.40	2.80	3.10	4.40	0.56
Platelets (140 to 440 platelets/nL) [†]									
Azide	21	233.00	40.107	149.00	206.00	230.00	268.00	304.00	—
Perchlorate A	14	235.07	47.798	159.00	204.00	245.00	270.00	317.00	0.89
Perchlorate B	8	221.88	61.989	144.00	182.50	213.00	246.00	348.00	0.57
Perchlorate C	15	230.53	57.679	127.00	193.00	222.00	258.00	343.00	0.88

* t Tests were performed assuming unequal variances based on Bartlett's test for equal variances (at an α level of 0.05).

[†] Values in parentheses represent the laboratory's normal range.

between the groups in the distributions of any of the other 12 chemical-profile parameters.

Perchlorate Excretion Rate

Urinary perchlorate levels for two workers in the high-exposure perchlorate group were monitored during 3 days with measurable occupational perchlorate exposure and during the subsequent 3 days without known perchlorate exposure (Fig. 2). The data indicate that the perchlorate body burden, as indicated by urinary perchlorate concentration, increases over the 3 days of work exposure, with (generally) a decrease between the 12-hour work shifts. Figure 2 graphically illustrates that exposure is the reason for absorption. Figure 3 presents the same data but presents it as the logarithm of the urinary perchlorate concentration. The elimination of perchlorate after the last definite exposure period appears to follow a first-order kinetics pattern, which is particularly noted when

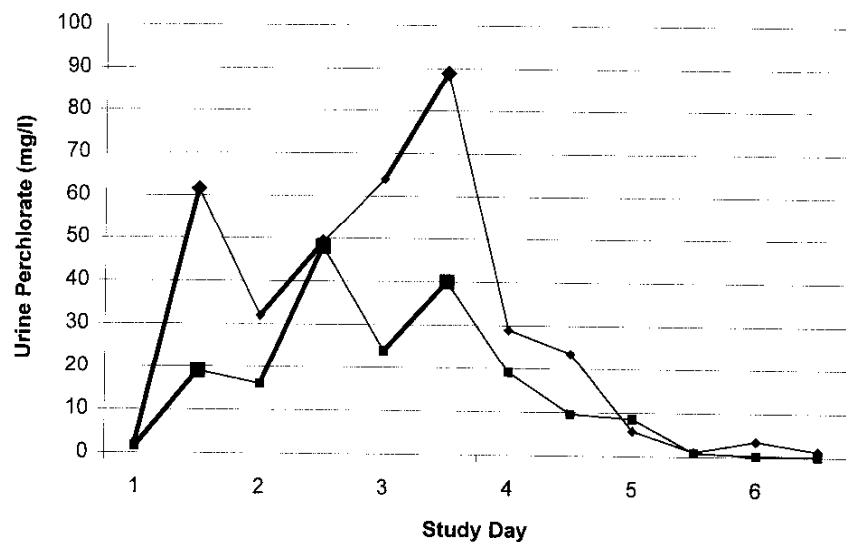


Fig. 2. Urinary perchlorate concentration (mg/L) every 12 hours (exposure periods are shown in bold). ♦, employee A; ■, employee B.

the urinary perchlorate level is between 0.1 and 10 mg/L (Fig. 3). The average perchlorate elimination half-life post-exposure for employee A was 7.9 hours (excluding

the period in day 6 of apparent minimal exposure), and the average perchlorate elimination half-life post-exposure for employee B was 8.2 hours. The graph of Fig. 3

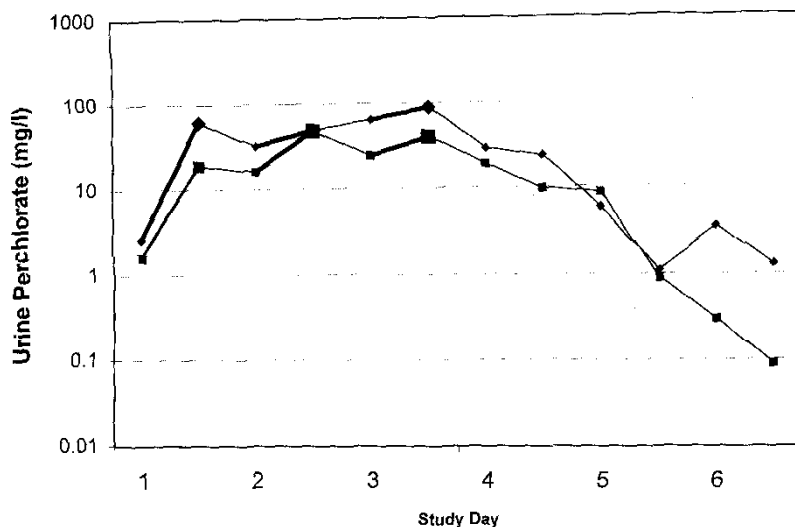


Fig. 3. Urinary perchlorate concentration (mg/L) every 12 hours (exposure periods are shown in bold). ♦, employee A; ■, employee B.

suggests that the excretion half-life may be longer when the urine concentration is greater than 10 mg/L than at lower levels, possibly indicating a redistribution into an alternative component site, such as the digestive tract.

Discussion

This occupational health study was conducted to determine whether occupational exposure to airborne perchlorate particles and the resultant systemic absorption of perchlorate during the manufacturing process has adversely affected the thyroid status of perchlorate workers. The study revealed no differences in thyroid-function tests between perchlorate workers and a comparison group (azide workers). No differences in thyroid-function test results were found among the workers across the four exposure groups.

The perchlorate characteristics of these four groups can be described in terms of airborne perchlorate exposure and of perchlorate absorption as determined from urinary perchlorate excretion. Based on industrial hygiene airborne measurements, these groups are found to have had exposures with group arithmetic mean exposures ranging from 0.01 to 60

mg perchlorate per day, group median exposures ranging from 0.01 to 45 mg/day, and group geometric mean exposures ranging from 0.01 to 30 mg perchlorate per day. Different analysts may consider different exposure metrics to best summarize the airborne exposure. Based on urinary perchlorate excretion data, these groups are found to have had absorbed dosages with means ranging from 0.9 to 34 mg/day and medians ranging from 0.6 to 33 mg/day. The dosage data distribute symmetrically about the means, and the means are almost identical to the medians. Therefore, geometric means would provide no additional information. These data demonstrate no adverse effect on thyroid function at perchlorate absorptions of 0.01 to 34 mg/day.

No occupational thyroid disease was found among these workers. The perchlorate exposures in this plant were not found to be associated with thyroid abnormalities. Furthermore, there was no evidence of differences between the groups with respect to renal, hepatic, or hematological parameters. Thus there is no evidence that perchlorate affects the thyroid or those other three systems at these

absorption levels, a daily absorption of 34 mg/day.

This study is the first to measure and assess urinary perchlorate concentrations in workers exposed to perchlorate particles. This study includes two measures of perchlorate exposure (total and respirable particles) and one measure of perchlorate absorption (urinary perchlorate). The two measures of perchlorate exposure have been found to correlate very strongly (Fig. 1). Data analysis has been conducted to examine the relationship between airborne particle perchlorate (both respirable and total) and perchlorate absorption.

Figure 4 demonstrates the statistically significant association (correlation) between airborne respirable-particle perchlorate exposure and perchlorate absorption. The slope of the association ($b = 2.06$) is greater than 1, indicating that although the rise in respirable particle exposure significantly tracks the rise in absorption, the increase in absorption is twice as great as the increase in this exposure metric. Thus the respirable-particle perchlorate exposure is insufficient to account by itself for the rise in the perchlorate absorption.

Figure 5 demonstrates the statistically significant association (correlation) between airborne total-particle perchlorate exposure and perchlorate absorption. In this case, the slope of the association ($b = 0.31$) is less than 1, indicating that the increase in total-particle perchlorate exposure is sufficient to account for the increase in the perchlorate absorption. This analysis suggests that an absorption coefficient of 31% could describe the association between total-particle perchlorate exposure and perchlorate absorption. Inspection of Fig. 5 suggests that at lower total-particle perchlorate exposures (ie, 0 to 50 mg/day) other factors, such as hand-to-mouth ingestion, may make a major contribution to the total perchlorate exposure and absorption.

The airborne total-particle perchlorate, with its high aqueous solubility, appears to be readily absorbed

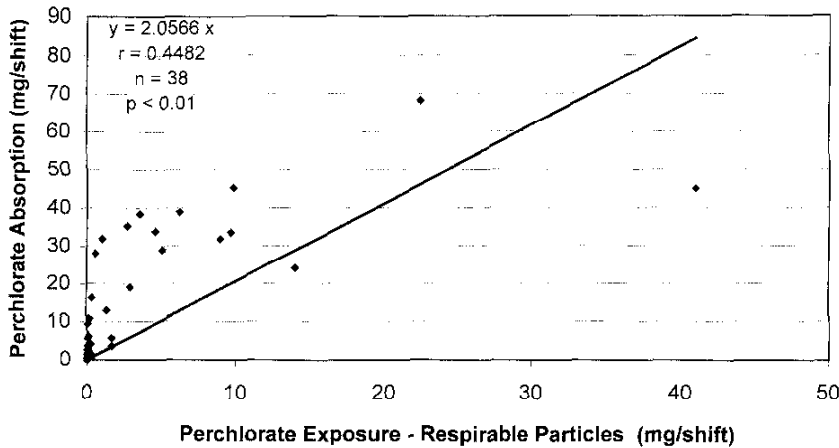


Fig. 4. Comparison of perchlorate absorption and respirable-particle perchlorate exposure.

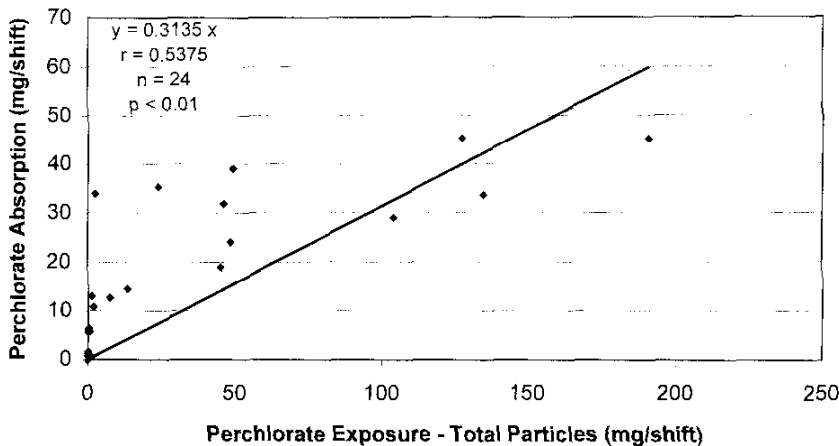


Fig. 5. Comparison of perchlorate absorption and total-particle perchlorate exposure.

and appears generally to be the source of the excreted perchlorate. The design of pre- and post-shift urine collections and perchlorate assessments and measurements of both respirable particle and total-particle inhalation exposure to perchlorate throughout the shift has revealed that total-particle (as well as respirable-particle) perchlorate inhalation exposure leads to systemic absorption of perchlorate and to its urinary excretion. The lower respiratory tract is the primary site for the absorption of respirable-particle perchlorate. Whether the total-particle perchlorate is also absorbed in the upper respiratory tract and is carried by mucus into the gastrointestinal tract, or it enters the gastrointestinal tract

by direct contact, is not important to the post-absorption pharmacology. The perchlorate absorbed into the bloodstream (whether from the respiratory or gastrointestinal tract) is equivalent since perchlorate excretion in the urine and its pharmacological effects on the thyroid are both dependent upon absorption into the bloodstream.

The data from the workers in this study contribute to the developing literature on perchlorate excretion rates in humans. The excretion half-lives of 7.9 hours and 8.2 hours in the workers observed for 3 days post-exposure is quite consistent with the 6 to 8 hours reported by Eichler in 1929³ and the 5 to 9 hours reported by Durand in 1938.⁴ There

is a quiet pleasure in observing that one's work replicates data published 60 to 70 years earlier, although the total number of subjects published is now only four.

The Eichler³ exposure was to a single oral dose of 1 or 2 grams. The Durand⁴ exposure was to a single oral dose of 0.8 grams. The two workers in the study presented here had been working in perchlorate production area C during the prior work period and can be assumed to have had the equivalent of a 34-mg oral dosage over a 12-hour period. Since these workers are regularly employed in this type of position, this exposure can be described as chronic or sub-chronic exposure at a moderate dosage (greater than environmental and less than pharmaceutical). Although there is a suggestion within our data that some other physiological processes may be occurring at higher exposure levels, these data do indicate that 8 hours is a reasonable estimate of the perchlorate excretion rate in humans. This 8-hour half-life has been consistent down to the limit of detection in the urine.

This study has provided an insight into the absorption and excretion of perchlorate among workers exposed to airborne perchlorate particles. It has also shown that no adverse effect has been demonstrated on any of the workers' thyroids at these occupational exposure levels at this perchlorate manufacturing plant. This study also confirms the findings of Gibbs et al¹⁶ that demonstrated the absence of an adverse effect on thyroid function among perchlorate manufacturing employees at a different plant. Gibbs et al demonstrated the absence of an effect on thyroid function by examining across the work shift acutely and across the working life cumulative exposure chronically. Gibbs et al also demonstrated the absence of an effect on kidney, liver, or bone marrow function across the working life. The study presented here has added observations of individual respiratory perchlorate particle exposures and

subsequent urinary perchlorate measurements to the exposure measurements of Gibbs et al. It has also added serum T₃ and anti-TPO antibodies and a clinical thyroid examination to their assessment of thyroid-function outcome measures. This study has also reported the absence of an effect on the liver, kidney, or blood cells at a range of perchlorate exposure and absorption rates. Both studies have demonstrated that occupational exposures to perchlorate have not been hazardous to the thyroid health status of the workers studied at these plants or to the other examined organ systems.

Occupational health studies serve to advise workers, physicians, and managers on the safe limits of exposure. That is their primary function and their purpose of design. Such studies may also be helpful to toxicologists and other health scientists who desire clarification of mechanisms and parameters concerning perchlorate exposure, absorption, toxicity, and excretion. Additionally, such studies are useful to environmental health specialists who must consider the risks associated with low-level exposures to perchlorate, either through inhalation or ingestion. The US Environmental Protection Agency and a number of state health departments are currently attempting to assess the potential magnitude of risk associated with various levels of perchlorate contamination of drinking water. Studies such as this provide useful information for the assessment of such risks.

Current levels of perchlorate detected in the drinking water of southern California and southern Nevada are in the range of 5 to 8 ppb ($\mu\text{g/L}$) and up to 15 ppb, respectively. The assumed ingestion of 2 liters per day would yield an ingestion exposure and absorption of up to 30 μg perchlorate per day for an adult. This rate is approximately one to two orders of magnitude lower than that of the azide worker control group in this study. It is approximately three orders of magnitude lower than that

of the perchlorate group C workers, who showed no adverse effect on their thyroid health status with recurrent occupational absorbed exposures of approximately 34 mg perchlorate per day.

Two issues of perchlorate toxicity have arisen: hematotoxicity in adults and congenital hypothyroidism in the newborn. Cases of hematotoxicity associated with perchlorate exposure have generally been reported for Graves' disease patients being treated therapeutically with exposures of 1000 mg per day or greater, occasionally at 600 mg per day, and only once in a patient at 450 mg per day (who had previously shown a toxic reaction at 800 mg per day¹⁷). No hematotoxicity was seen among the workers in the study presented here and, in particular, not at 34 mg per day. The case-report literature suggests that reported hematotoxicity findings in Graves' disease patients may occur at exposures at least one to two orders of magnitude greater than the occupational exposures and at least four to six orders of magnitude greater than the environmental exposures from the southern California and Nevada waters.

Prior to 1960, perchlorate was commonly used to treat women with hyperthyroidism during pregnancy. Crooks and Wayne¹⁸ reported in *Lancet* that they had "treated 12 pregnant thyrotoxic patients with potassium perchlorate (600 mg/day or 1000 mg/day) and in each have achieved satisfactory control of the disease. One of the infants had a very slight enlargement of the thyroid that disappeared within 6 weeks. The remainder showed no abnormality of any kind." This is the only published report regarding perchlorate and the neonatal thyroid. Additionally, the California Department of Health Services¹⁹ has a preliminary health review for a Superfund site in Sacramento, California, where perchlorate is a contaminant of concern. They found no increase in congenital hypothyroidism in the zip codes of interest. Similarly, Lamm and Do-

emland²⁰ reported that the counties in southern California and Nevada with perchlorate-contaminated drinking water had no more cases of congenital hypothyroidism than would be expected, based on state rates for 1996 and 1997. Thus only one case of transient goiter in a newborn has been reported for those whose mothers had therapeutic exposures, and two research groups looking at different geographic areas found no evidence of an increased risk of congenital hypothyroidism with environmental exposures.

In conclusion, this study has (1) found no evidence of an adverse effect of perchlorate exposure on thyroid health status among perchlorate workers, (2) demonstrated that airborne perchlorate is absorbed and excreted by perchlorate workers, (3) indicated that the exposure to perchlorate particles larger than respirable size is likely to account for the magnitude of perchlorate excretion, (4) provided an estimate for the urinary excretion half-life of perchlorate in perchlorate workers, and (5) developed information that may be useful in the assessment of human risk from environmental exposure to perchlorate. The results of this study do not support the hypothesis that chronic exposure to perchlorates at the levels encountered in this study has an effect on thyroid function. There also is no evidence to support the hypothesis that perchlorate has an effect on the hematopoietic system, even at these occupational doses. The findings in this study demonstrate a "no adverse effect level" on thyroid function and hematotoxicity in a worker population of 34 mg perchlorate per day for humans.

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