HETA 88-199-2071
OCTOBER 1990
GATES ENERGY PRODUCTS, INC.
GAINESVILLE, FLORIDA

NIOSH INVESTIGATORS:
Richard R. Hammel, M.D., M.P.H.
Stephen L. Klincewicz, D.O.
Paul Roper, CIH
Alice L. Greife, Ph.D.
Anne T. Fidler, Sc.D.

## I. SUMMARY

On March 10, 1988, the National Institute for Occupational Safety and Health (NIOSH) received a request for technical assistance from the Occupational Safety and Health Administration (OSHA) to evaluate possible adverse health effects among workers exposed to nickel and cadmium dusts in the manufacture of nickel-cadmium batteries at Gates Energy Products, Incorporated, Gainesville, Florida. In response to this request, NIOSH investigators conducted an initial survey April 12-13, 1988, which included a walk-through survey, discussions with management and union representatives, and a review of the company's environmental and biological (urine) monitoring data for nickel and cadmium collected over the past several years.

Medical surveys were conducted in February and October 1989 after review of the company's extensive environmental and biological data (obtained during the initial site visit) indicated that the pressed plate, plate preparation, and plate-making areas of the plant had the highest potential for worker exposure to cadmium. The purpose of the first medical survey was to evaluate various indicators of renal and immunologic status in male workers exposed to cadmium and nickel dusts in the plate-making and pressed plate area of the plant. However, the cadmium-exposed male workers also had high exposures to nickel, which is also considered a potential nephrotoxin. Little information in the literature exists about the possible synergistic or antagonistic effects of heavy metals on renal function. The purpose of the second survey was to evaluate areas with minimal exposure to nickel but with either low or high exposures to cadmium.

Over-exposure to cadmium was clearly evident in cadmium-exposed workers for both surveys. Nine of 39 (23%) cadmium-exposed workers in the February 1989 medical survey had urine cadmium levels greater than 10 ug/g creatinine. In the October 1989 medical survey, 13 of 47 (28%) workers in the low and 21 of 49 (43%) workers in the high cumulative airborne cadmium exposure groups had urine cadmium levels greater than 10 ug/g creatinine. In the February 1989 medical survey, three of the 39 cadmium-exposed workers (8%) demonstrated evidence of cadmium-induced abnormal renal function using three screening tests [urine albumin, beta-2-microglobulin (B2M), and retinol binding protein (RBP)]. Of these three workers, two had elevated urine levels of albumin alone, while the other also had elevated urine levels of RBP and B2M. (All elevated levels were defined by the arithmetic mean of the creatinine-standardized measurements in the unexposed plus two standard deviations.) Similar results were found in the October 1989 medical survey. Three of 91 cadmium-exposed workers (3%) had elevated urine levels of albumin while none had elevated levels of urine RBP. None of the 6 workers described had known non-occupational causes of renal dysfunction (e.g., diabetes, hypertension). In comparison, of the 69 unexposed workers evaluated in both surveys, none had evidence of abnormally high levels of urinary proteins.

No consistent differences in urine proteins were observed between the cadmium-exposed and non-exposed groups in this analysis of either the February or October 1989 medical surveys. In addition, cumulative airborne cadmium levels did not have a significant relationship with any measure of renal function used in our investigation. However, in both surveys, the analysis of cadmium-exposed workers with urine cadmium levels greater than 10 ug/g creatinine (compared to those with less than 10 ug/g creatinine) clearly suggests that the group with higher exposure did have modest elevations of the urinary high-molecular-weight protein albumin, and the low-molecular-weight proteins RBP, NAGA, and AAP, consistent with mild glomerular and tubular dysfunction as reported by others in similarly exposed workers.

Thus, it appears from our investigation that cadmium-induced renal dysfunction is evident with current available and recommended screening tests in this study population. This investigation also demonstrates that subclinical effects such as significant increases in mean levels of urinary tubular enzymes NAGA and AAP are apparent in cadmium-exposed workers with urine cadmium levels above 10 ug/g creatinine compared to those below this level.

On the basis of this investigation, NIOSH investigators concluded that a health hazard from overexposure to cadmium dust exists at the Gates Energy Products, Inc., Gainesville, Florida plant. NIOSH recommends that exposure to cadmium in any form be restricted to the lowest concentration feasible based on evidence that cadmium is a potential human carcinogen. Recommendations regarding medical monitoring are presented in Section VIII of this report.

Keywords: SIC 3691 (Storage batteries), nickel, cadmium, nickel-cadmium batteries, urinary cadmium, renal tubular enzymes, n-acetyl glucosaminidase, NAGA, alanine aminopeptidase, AAP

## II. INTRODUCTION

On March 10, 1988, the National Institute for Occupational Safety and Health (NIOSH) received a request for technical assistance from the Occupational Safety and Health Administration (OSHA) to evaluate possible adverse health effects among workers exposed to nickel and cadmium dusts in the manufacture of nickel-cadmium batteries at Gates Energy Products, Incorporated, Gainesville, Florida. In response to this request, NIOSH investigators conducted an initial survey on April 12-13, 1988, which included a walk-through survey, discussions with management and union representatives, and a review of the company's environmental and biological (urine) monitoring data for nickel and cadmium collected over the past several years.

Medical surveys were conducted in February and October 1989. The purpose of the first medical survey was to evaluate various indicators of renal and immunologic status in male workers exposed to cadmium and nickel dusts in the plate-making and pressed plate area of the plant. However, the cadmium-exposed male workers also had high exposures to nickel, which is also considered a potential nephrotoxin. Little information in the literature exists about the possible synergistic or antagonistic effects of heavy metals on renal function. The purpose of the second survey was to evaluate areas with minimal exposure to nickel but with either low or high exposures to cadmium.

Preliminary results were reported to OSHA, the company and the union on May 26, 1988 (initial walk-through), September 1989 (Interim Report No. 1 - February 1989 medical survey), and April 19, 1990 (October 1989 medical survey).

## III. BACKGROUND

### A. Plant History and Workforce

Gates Energy Products, Inc., Gainesville, Florida, manufactures a variety of rechargeable nickel-cadmium cells and batteries for industrial and consumer applications. The plant was originally built by the General Electric Co. (GE) in 1963, and owned and operated by GE until January 1987, when Gates purchased the facility. The hourly workforce and many of the administrative and management staff have been retained by Gates. From 1977 until 1982, rechargeable sealed lead cells and batteries were also manufactured at this plant.

The facility employs approximately 1080 production workers and 190 maintenance workers. The plate-making areas have approximately 350 production workers and 60 maintenance workers. The workforce is predominantly female, particularly machine operators involved in making pressed plates, plate preparation, winding, cell assembly, and testing. The plant uses a rotating shift schedule involving four sets (or shifts) of workers, most on 12-hour work shifts, alternating 3- and 4-day work weeks.
In 1977, the plant began an extensive environmental and biological monitoring program which includes pre-employment baseline data and personal exposure data for airborne cadmium and nickel, and corresponding urinary cadmium and nickel levels. The data base has been maintained and continuously supplemented up to the present time. The air and urine monitoring data are computerized and accessible to Gates staff for a variety of analyses. In 1988 alone, over 1,000 personal exposure air samples were obtained and added to the data base.

### B. Process Description

The manufacture of nickel-cadmium cells involves a number of processes: perforation, nickel plating, nickel slurry, sintering, impregnation, electrochemical cleaning, preparation of pressed plates (another type of negative electrode), plate preparation, cell assembly (winding, filling, and closing the cells), and testing.

#### 1. Plate-making (Sintered Plates)

The structural substrate for the plate is carbon steel. In the perforation area, rolls of carbon steel are unwound and perforated (holes are punched in the steel sheets). The next step is nickel plating, where

the perforated steel strip is washed in an alkaline solution, rinsed, pickled in sulfamic acid, and passed through plating baths where the steel is plated with nickel from a nickel sulfamate/nickel bromide solution. The nickel-plated steel strips are used for producing both positive and negative plates. Most employees in the plate-making department are men.

A slurry containing metallic nickel powder is prepared in the slurry room. A layer of the slurry is applied to the nickel-plated strip and passed through sintering ovens in a reducing atmosphere where the slurry is dried and the nickel powder is annealed.

The sintered strips are then impregnated with either nickel nitrate solution (for the positive electrode) or cadmium nitrate solution (for the negative electrode), treated with sodium hydroxide, washed, and dried.

The strips are then brushed and washed in an electrochemical cleaning operation where the strips are immersed in sodium hydroxide solution.

2. Pressed Plate

An alternative to the impregnated, sintered negative plate is a cadmium oxide pressed plate. In the Pressed Plate area, a paste is prepared containing cadmium oxide. The substrate for the pressed plate is the nickel-plated, perforated carbon steel strip described previously. The strip is stippled and cut, and a metal tab may be attached. Operators wearing gloves apply the paste to the strip at the pasting machines. The pasted strips are dried, cut (slit) into narrower strips, and rewound. Most machine operators in the pressed plate area are women. Men perform mostly machine set-up, adjustment, and maintenance.

3. Plate Preparation

In the plate preparation department, electrode strips are slit, cut, or punched, and inspected at downdraft tables. Most machine operators are women.

4. Cell Assembly (including Winding & Closing)

In the winding operation, the negative and positive electrode plates are wound with paper separators to form cells. The cells are put inside nickel-plated steel cylinders, and potassium hydroxide electrolyte is added. The cells are sealed closed, charged, tested, and inspected.

## IV. EVALUATION DESIGN AND METHODS

### A. Environmental

To evaluate current exposure levels, printouts were obtained from the company's computerized health and safety database listing all personal exposure sampling results for 1988. This included 1030 personal samples for nickel and cadmium. [The company data were reported as 8-hour time-weighted averages (TWAs). However, there was no indication whether these were based on actual 8-hour measurements or represented 12-hour samples calculated as 8-hour TWAs.] Twenty-seven job categories, workstations, or operations were selected for analysis from the Plate-making, Pressed Plate, Plate Preparation, and Winding & Closing departments.

Printouts of the company's sampling results were sorted by department and by either job title or workstation. Considerable manual compilation was also necessary due to lack of consistent workstation terminology. The paste preparation processes in the Pressed Plate Department included job titles and workstation locations designated in the database as paste making, mixing, blending, weighing, big mixer, and small mixer. Paste machine operators were grouped to include all the various types of paste application machines designated by different names in the database. The waste recovery operations were grouped,

including jobs/operations designated as rework, reclaimer, and shaker. Materials handling included jobs listed as moveman or moveperson. Sintering furnace included jobs/operations listed as furnace, horizontal furnace, vertical furnace, and sintering furnace. Impregnation included listings of "imp. lines" as well as individual line numbers identified by company personnel as impregnation lines. Maintenance jobs included mechanics, electricians, machinists, welders (not tab welding machines), blade adjusters, tool makers, and sometimes machine set-up. Sorting and stacking included operators working at machines designated by a press tonnage.

For each of the 27 jobs/operations analyzed, personal sampling data for 1988 were statistically analyzed to compute mean, median, standard deviation, and range. Subsequently, the jobs/operations were ranked according to their mean cadmium and nickel concentrations. Occasionally, a single value considerably higher than the other samples (a possible outlier) elevated the mean considerably above the median. Consideration was given to ranking the jobs by median as perhaps more typical of the usual exposure range; however, this was found to have little effect on the overall job exposure ranking, and was thus not pursued.

B. Medical

1. February 1989 Medical Survey

a. Participant Selection

As part of the preliminary investigation, a review of the company's extensive environmental and biological data indicated the pressed plate and plate-making area of the plant had the highest potential for worker exposure to both nickel and cadmium. Since we wished to compare these results to other studies, only male workers were selected to participate in the initial study.

From a potential list of 42 male day-shift workers with approximately 10 years of work experience (in cadmium-exposed areas) at the company, we were able to obtain participation from 40 (95%) employees. From a potential list of 43 male salaried employees with at least 10 years of work experience (in cadmium and nickel non-exposed areas) at the company, participation was obtained from 39 (91%) employees to serve as a referent population.

b. Survey instruments (methods)

The study consisted of a questionnaire; measurement of height, weight, and blood pressure; collection of a "spot" first-voided morning urine and fasting serum samples. The questionnaire collected information about characteristics such as age, history of diabetes, hypertension, smoking, non-steroidal anti-inflammation drug use, and previous occupational exposures to cadmium, lead, and solvents.

Biologic markers were selected to assess several types of renal function. All urine test results were creatinine-standardized to adjust for variations in urine concentrations. Indices of renal tubular function included urinary excretion of phosphorous, and the low-molecular-weight proteins, beta-2-microglobulin (B2M) and retinol-binding protein (RBP). Increased urinary excretion of these biologic markers can indicate renal tubular dysfunction.

Markers of renal tubular injury (or recent cellular damage) included the urinary brush border membrane enzymes alanine aminopeptidase (AAP), gamma glutamyl transferase (GGT), and the lysosomal enzyme N-acetyl glucosaminidase (NAGA). Increased urinary excretion of the enzymes in association with high urine cadmium levels is thought to indicate increased sloughing of membranes and organelles due to tubular dysfunction or increased cell turnover with necrosis and regeneration.

Measurements reflecting glomerular function were serum creatinine (which increases as the

glomerular filtration rate decreases), and urine albumin (which can increase with abnormal glomerular permeability to macromolecules).

Complete blood counts and measurements of serum immunoglobulins IgG, IgA, IgM were obtained. The blood counts were processed at a local university hospital laboratory within 4 hours of collection. The population of specific lymphocyte subpopulations and number of natural killer cells were determined using a fluorescent activated cell sorter. Natural killer cell activity, at two effector/target ratios, was determined at a NIOSH laboratory in Cincinnati. Specimens were collected over a 4-day period, with approximately the same number of exposed and unexposed participants submitting specimens each day. Employees were given instructions to submit a first-voided specimen in the morning and were apprised of the necessity of showering and changing clothes prior to the morning testing.

c. Estimation of exposure

To estimate each worker's cumulative exposure to airborne cadmium and nickel, for the time period between 1977 and 1989, a retrospective exposure matrix, by work area and contaminant, was constructed. Exposure prior to 1977 was estimated with the 1977 exposure data, since no major changes had been made to the manufacturing operation before instituting industrial hygiene monitoring.

Each retrospective matrix, by work area and contaminant was constructed in the following manner. The data were first grouped by year. Arithmetic means were then calculated for each year for which data were available. These means were then evaluated for the presence of a statistically significant upward or onward trend. If such a trend was present, each mean was considered to be an independent event, and that value was used in the cell representing that year. For years in which data were not available, the means of the cells on either side of the empty cell(s) were averaged, and that value was used in place of the missing value(s). If a statistically significant trend was not present, all the data collected for all the years were averaged to create one mean for the entire time period.

Each worker's time-weighted airborne exposure (TWE) was calculated by multiplying the duration of exposure in a given work area ($t_i$) by the annual estimated airborne exposure for that work area and year ($E_i$) and then summing these values to obtain cumulative exposure. Because computed exposure days were done on the basis of elapsed calendar days and not on the basis of working days, the estimated cumulative exposure is multiplied by 240/365 (assuming an employee worked an average of 240 days/year) to obtain the final estimate of cumulative exposure.

Alternatively, urine cadmium levels are also a measure of chronic exposure to cadmium and are probably a better indicator of an individual's internally absorbed cadmium dose. Urine cadmium levels above 10 ug/g creatinine are considered to indicate over-exposure to cadmium. Thus, both measures of cadmium exposure were evaluated in this investigation.

d. Statistical Methods

All statistical methods, including comparison of means and correlations, were performed using the SPSS/PC-Plus Statistical package. Measured urine concentrations of metals, proteins, and enzymes were all creatinine-standardized for individual interpretation and statistical analysis. Two individuals with a urine creatinine of less than 50 mg/dL were excluded from the analysis since previous studies have shown such results to be unreliable. The urine and blood results of the exposed workers were compared with those of the unexposed workers. In addition, the exposed individuals were classified into two groups, according to whether their urine cadmium was above or below 10 ug/g creatinine. Reference ranges for all laboratory tests conducted are presented in Appendix A.

Urine and serum values for renal, hematologic, and immunologic parameters were all compared using student's t-test to test the difference between group means for continuous variables. Dichotomous variables were analyzed using a 2X2 contingency table and chi square or Fisher's exact test, as appropriate.

When an individual observation was not available, that datum was coded as a missing value. Clinical test results that were reported as being below the laboratory's limit of detection were recorded as 0.

2. October 1989 Medical Survey

a. Participant Selection

Based on 1988 airborne cadmium levels by department and job title, eligible participants were categorized into 3 groups according to cadmium exposure: none, low, and high. This a priori selection of participants was done prior to calculation of cumulative cadmium exposure. Almost all participants had at least 10 years of work experience.

b. Survey instruments (methods)

The study consisted of a questionnaire; measurement of height, weight, and blood pressure; collection of a "spot" first-voided morning urine and fasting serum samples. The questionnaire collected similar demographic and medical information as administered in the February 1989 survey (see section IV. B. 1. b.).
Biologic markers to assess several types of renal function were similar to those selected in the February 1989 survey. All urine test results were creatinine-standardized to adjust for variations in urine concentrations. Indices of renal tubular function for this survey included urinary excretion of calcium, phosphorous, glucose and the low-molecular-weight protein, retinol binding protein (RBP). Urinary excretion of B2M was not measured in this survey.

Markers of renal tubular injury (or recent cellular damage) included the urinary brush border membrane enzymes alanine aminopeptidase (AAP), gamma glutamyl transferase (GGT), and the lysosomal enzyme N-acetyl glucosaminidase (NAGA).

Measurements reflecting glomerular function were serum creatinine and serum urea nitrogen (both of which increase as the glomerular filtration rate decreases), and urine albumin and total protein (both of which can increase with abnormal glomerular permeability to macromolecules).

c. Estimation of exposure

Estimates of each worker's cumulative exposure to airborne cadmium and nickel were calculated using the industrial hygiene measurements obtained by the company for the various departments from 1977-1989 (as described previously in section IV. B. 1. c.). Urine cadmium levels were also used as a measure of chronic exposure to cadmium (see section IV. B. 1. c.).

d. Statistical Methods

All statistical methods, including comparison of means and correlations, were performed using the SAS for Personal Computers (version 6.03) statistical package. Measured urine concentrations of metals, proteins, and enzymes were all creatinine-standardized for individual interpretation and statistical analysis. Ten individuals (5 cadmium-exposed, 5 non-exposed) with urine creatinines of less than 50 or greater than 300 mg/dL were excluded from the analysis of renal function tests since previous studies have shown such results to be unreliable.

The urine and blood results of the low and high cadmium-exposed workers were compared with those of the nonexposed workers. In addition, the cadmium-exposed individuals were classified into two groups, according to whether their urine cadmium was above or below 10 ug/g creatinine. Reference ranges for all laboratory tests conducted are presented in Appendix A.
Urine and serum values for renal parameters were all compared using student's t-test or analysis of variance to test the difference between group means for continuous variables, as appropriate. Dichotomous variables were analyzed using a 2X3 contingency table and chi square or Fisher's exact test, as appropriate.

When an individual observation was not available, that datum was coded as a missing value. If a specific measurement (either clinical test or industrial hygiene monitoring result) was reported as below the level of detection (LOD), the individual's result was calculated as the LOD value divided by the square root of two. This was done to minimize bias of either assigning a value of zero or the LOD, since the true value of the observation probably lies in between either of these endpoints. This method is useful for producing good estimates of both the mean and standard deviation for a given test when the data are not highly skewed (eg. geometric standard deviation less than 3.0).[1]V.

## V. EVALUATION CRITERIA

### A. Cadmium

Cadmium is a heavy metal used in the manufacturing of batteries, pigments, and jewelry, and as a neutron absorber in nuclear reactors. Cadmium may enter the body either by ingestion (swallowing) or inhalation (breathing) of cadmium metal or oxide.

Cadmium acetate, chloride and sulfate are soluble in water, while cadmium oxide and sulfide are almost insoluble.[2]

1. Absorption and Measurement

Approximately 6 to 10 percent of ingested cadmium and 15 to 30 percent of inhaled cadmium is absorbed into the body.[3] Cadmium is transported from the site of absorption by red blood cells and plasma. It is deposited in organs throughout the body, but major deposition occurs in the

liver and kidneys. Metallothionein is believed to be the chief protein responsible for cadmium t

ransport in the blood.[2]

Under normal conditions, the kidneys accumulate the greater concentration of cadmium. The estimated half-life of cadmium is extremely long, approximately 10-30 years, so that most of the cadmium absorbed in the body is retained.[4] Cadmium is excreted from the body very slowly and thus accumulates in the cortex of the kidney over a lifetime. However, the urine concentration of cadmium may greatly decrease with the progression of interstitial fibrosis and chronic renal disease so that the urine concentration of cadmium is not a useful indicator of renal cadmium in the presence of severe cadmium nephropathy.

The blood concentration is the best indicator of recent cadmium exposure and absorption (mainly the last few months).[5,6] The blood cadmium level in the general population is less than 7 micrograms (ug) per deciliter (dL) of whole blood. Chronic cadmium exposure can be assessed by measuring the cadmium content of the kidneys through the technique of neutron activation analysis.[7] The urine cadmium concentration, a widely used index of exposure, is primarily an indicator of chronic exposure. In the general population, the average urinary cadmium level is 0.35 ug/g creatinine, and values above 2 ug/g creatinine are exceedingly rare.[8]

An increase in urine cadmium concentration may occur for two reasons. First, short-term, high levels of exposure to cadmium may result in increased blood levels and overflow excretion (increased clearance) by the kidney.[4] Such exposures exceed the ability of the liver and kidney to bind and retain cadmium by metallothionein in these tissues. Peak increases in clearances are usually related only to very acute excessive exposures and the increase in urine is transient. Second, an increase in urine cadmium concentration may also reflect renal tubular dysfunction, resulting in a decrease in the ability of renal tubular cells to absorb cadmium.[9] Cadmium in glomerular filtrate is usually bound to metallothionein which is a low-molecular-weight protein and thus may compete with other low-molecular-weight proteins for reabsorption by renal tubular cells.

2. Acute Toxicity

Acute inhalation exposure to cadmium can cause pneumonia or pulmonary edema, as well as liver and kidney damage.[10, 11] Ingestion of toxic quantities can produce nausea, vomiting, and diarrhea. Exposure to an airborne concentration of 40 $mg/m^3$ is considered immediately dangerous to life.

3. Chronic Toxicity

Occupational exposure to cadmium is usually chronic. Chronic occupational exposure to cadmium can produce several toxic effects, of which the most important are emphysema and kidney disease.[2] Also, occupational exposure has been associated with cancer of the prostate gland, and there is evidence that cadmium exposure may be associated with lung cancer.[12-14]
Kidney disease is one of the effects of cadmium exposure which has aroused considerable concern. There is debate in the literature about the level of cadmium exposure which, over a period of time, will cause kidney damage among individuals occupationally exposed. The initial signs of cadmium nephropathy (kidney damage) are subtle. Affected workers will usually have no symptoms in the early stages, and their kidney function tests may still be within the broad range of normal. Cadmium associated renal disease may continue or develop long after exposure to cadmium ceases.[15]

Because of kidney has an enormous reserve capacity, results of the usual renal function tests (blood urea nitrogen (BUN), serum creatinine, and serum uric acid) will not become frankly abnormal until one-third to one-half of the kidney's capacity has been destroyed.[16] For that reason, more sensitive tests of renal dysfunction have been sought. These tests include urinary low-molecular-weight protein excretion such as beta-2-microglobulin, retinol-binding protein, renal brush border enzymes (such as AAP, GGT, NAGA), and determination of phosphate, calcium, glucose, and amino acid excretion.

4. Environmental

a. Biological monitoring

Both blood and urine cadmium are potentially useful for detecting excessive exposure prior to the development of renal tubular damage, though neither is completely reliable for this purpose. Based on currently available data, guidelines have been developed by various expert bodies (NIOSH 1976, World Health Organization (WHO) 1980, American Conference of Governmental Industrial Hygienists (ACGIH) 1989) which suggest that, to prevent renal dysfunction (primarily renal tubular proteinuria) in workers exposed to cadmium, the concentration of cadmium should not exceed 10 ug/g creatinine (approximately 10 ug/Liter).[17-19]

The ACGIH and the WHO have also recommended that cadmium in the blood not exceed 10 ug/L, in order to prevent potential renal damage.[18, 19] The WHO also recommended, as an action level, that if the individual urine cadmium level exceeded 5 ug/g creatinine, control measures should be applied. The WHO recommendations were based on signs of renal disturbance found in workers exposed to cadmium and included the following: (1) increased proteinuria; (2) increased renal clearance of specific proteins (B2M, RBP, albumin, transferrin, and IgG); (3) increased plasma urea and creatinine; and (4) perturbation of some functional tests such as creatinine clearance.[19] However, there are insufficient data to evaluate whether limiting cadmium in the urine or blood is protective against cancer.

b. Environmental standards

The NIOSH recommended exposure limit (REL) for cadmium dust is that employers reduce occupational exposure to the lowest feasible limit (LFL). This is based on the NIOSH recommendation that cadmium and its compounds be considered as a potential occupational carcinogen.[20] The ACGIH Threshold limit value (TLV) is currently 50 ug/m$^3$ as an 8-hour time-weighted average (TWA), but the 1988-89 edition includes a notice of intention to reduce the cadmium TLV to 10 ug/m$^3$ and to designate cadmium as a suspected human carcinogen.[21] The current OSHA Permissible Exposure Limit (PEL) is an 8-hour time-weighted average (TWA) of 200 ug/m$^3$ (cadmium dust), although an interim protection measure of 50 ug/m$^3$ is currently being enforced. A new standard for cadmium has been recently proposed by OSHA which would reduce the PEL to an 8-hour TWA of either 1 or 5 ug/m$^3$.[22]

B. Nickel

Inorganic nickel is a silver-white metal, and nickel salts are crystals.[23] Inhaled nickel is absorbed in the lung better than in the gastrointestinal tract, and the amount of nickel absorbed depends on the type of nickel compound.[24] The potential and reported health effects due to nickel include increased risk of gastric cancer, increased risk of sarcoma, chronic irritation of the upper respiratory tract manifested by rhinitis, sinusitis, perforation of the nasal septum, anosmia (loss of smell), pulmonary irritation and fibrosis, pneumoconiosis, asthma, and dermatitis.[25]

Even though available evidence indicates an association between human exposure to inorganic nickel and the development of cancer, the mixed exposures, both to different nickel compounds and to other elements frequently occurring in the workplace, have prevented complete differentiation of the effects of individual compounds. NIOSH has identified nickel as a suspect carcinogen because workers in the nickel industry have experienced excess lung and nasal cancers.[26]

Nickel accumulates in the kidney of test animals and can cause nephrotoxicity at high concentrations.[27] Blood and urine nickel are used to determine recent nickel exposure, but neither index reflects the body burden of nickel.[23]
The NIOSH recommended exposure limit (REL) for nickel is 0.015 mg/m$^3$ as a 10-hour TWA.[28] The ACGIH Threshold limit value (TLV) for metallic nickel is currently 1.0 mg/m$^3$ as an 8-hour time-weighted average (TWA), but the 1989-90 edition includes a notice of intention to reduce the nickel TLV to 0.050 mg/m$^3$ and to designate nickel as a confirmed human carcinogen.[29] The OSHA PEL for nickel is an 8-hour TWA of 1.0 mg/m$^3$.

VI. RESULTS

A. Environmental

1. Cadmium

Cadmium concentrations (personal samples only) are shown in Table 1, grouped by department or area. A relative ranking of the 27 job categories by mean air cadmium level is shown in Table 2. By far, the highest cadmium levels are in the Pressed Plate Department. The six highest exposure job categories were all from Pressed Plate. In fact, all 12 job categories analyzed in Pressed Plate were in the top 13 job exposure categories for cadmium. Four of the job categories, paste preparation, paste dipping (only 1 sample in 1988), paste machine operators, and process/machinery set-up, had mean cadmium exposures in excess of 100 $ug/m^3$. All mean concentrations in Pressed Plate exceeded 30 $ug/m^3$. The company's respirator policy required use of respirators for jobs whose exposure levels exceeded the permissible exposure limit (PEL) enforced by OSHA at the time. To compensate for 12-hour workshifts, Gates modified the OSHA PEL by reducing it by 33%. At the time of the NIOSH initial survey in April 1988, the company was using the OSHA PEL of 200 $ug/m^3$. At the time of the February 1989 NIOSH follow-up survey, the company was using the 1987-1988 ACGIH TLV of 50 $ug/m^3$ which OSHA was enforcing at that time. In the 1987-1988 TLV booklet, the ACGIH proposed to lower the TLV to 10 $ug/m^3$. Twenty of the 27 jobs analyzed had mean cadmium levels in excess of the proposed TLV of 10, including all jobs in Pressed Plate and Plate Preparation, 4 job categories in Plate-making, and the winding jobs in Winding & Closing.

The use of respiratory protection would certainly modify the amount of cadmium that actually enters the body. A respiratory protection policy was established at this company in 1977 that required the use of respirators while performing certain tasks within jobs. However, the level of detail in the work histories did not allow the documentation of the use of respirators among the workers in this study.

2. Nickel

Nickel concentrations (from personal sampling) are shown in Table 3, grouped by department or area. A relative ranking of 26 job categories by mean air nickel levels is shown in Table 4. One job category, dipping paste in Pressed Plate, did not have any air nickel monitoring conducted in 1988. The highest nickel exposures are found in Plate-making and Plate Preparation. Nickel slurry preparation and sintering furnace operation in Plate-making, and materials handling in Plate Preparation, had mean nickel concentrations above 100 $ug/m^3$, although the median exposures for sintering furnaces and materials handling were below 40, due to a single elevated sample in each of those job categories.

Sixteen of the 26 job categories analyzed had mean nickel concentrations above the 15 $ug/m^3$ NIOSH recommended exposure limit. These jobs included all job categories (that were analyzed) in Plate-making and Plate Preparation, plus the winding operation in Winding & Closing. All jobs in Pressed Plate had mean nickel concentrations below 15 $ug/m^3$, except for the slitting category. The company requires respirators be worn by workers in the nickel slurry room, the highest nickel-exposure job category.

B. Medical

1. February 1989 Medical Survey

a. Participants

Overall, 40 cadmium-exposed production workers and 39 non-exposed salaried employees participated in the survey. The results of one non-exposed individual were excluded from analysis since a later review of his employment history revealed that he had previously worked in the nickel-cadmium battery production area for 3 years. One individual from the exposed group did not submit urine specimen, so his results were not included in the study. The two individuals whose urine creatinine was too low to interpret accurately were also excluded from the analysis. In summary, one exposed individual and three unexposed individuals were excluded from analysis. Otherwise, if for technical reasons, a specific measurement was not obtained, an individual's result was treated as a missing value.

Demographic and other characteristics of the participants are shown in Table 5. The referent population was older (49.9 vs 41.9; t=–4.4, p=0.001), and had a greater proportion of white individuals (90% vs 49%; $X^2$=12.5, p=0.004), and reported more pack-years of smoking among those who smoked (20.2 vs 9.1; t=– 2.7, p=0.009).

The urine metal concentrations presented are corrected for creatinine. Cadmium-exposed workers demonstrated significantly higher levels of urine nickel and urine cadmium than the non-exposed group. Nine of the 39 cadmium-exposed workers (23%) had urine cadmium levels above 10 ug/g creatinine. None of the non-exposed employees demonstrated urine results above this level.

b. Medical History

Self-reported medical histories for selected medical conditions are shown in Table 6. Percentages are calculated only for those responding to the question. "Don't know" is classified as a missing response. The results were analyzed using a 2x2 contingency table with calculation of a chi-square or 2-tailed Fisher's exact test.

c. Urine and Blood Tests

Table 7 shows the arithmetic mean values of the results of the urine proteins, and renal function tests. All concentrations presented are corrected for creatinine. There were no differences between the exposed and unexposed group with respect to the renal enzymes AAP and NAGA. The unexposed workers had a statistically higher urine level of retinol binding protein than the exposed workers (1.0 vs 0.8 mg/g creat; p=0.02). The exposed workers demonstrated a higher mean serum creatinine level than the unexposed group (1.2 vs 1.0 mg/dL; p=0.001). Two of the exposed, and none of the unexposed, workers had levels of urine albumin (corrected for creatinine) over 20 mg/g creatinine, a value considered to be the upper level of normal.

Table 8 shows a similar analysis comparing exposed workers with high urine cadmium (greater than 10 ug/g creatinine) to those with lower values (less than 10 ug/g creatinine). The high urine cadmium group showed higher levels of NAGA (1.0 vs 0.6 U/g creat; p=0.03).

Table 9 shows the results of the hematologic and immunologic parameters studied. The exposed group demonstrated a higher total IgG (1231.4 vs 1035.9 mg/dL; t=3.0, p 0.0004) and a lower hemoglobin (14.8 vs 15.2 g/dL; t=–2.2, p=0.03) and MCHC (34.3 vs 34.6 g/dL; t=– 2.2, p=0.03).

Table 10 compares the immunologic and hematologic tests results between the high and low cadmium groups. The two groups showed no major differences for any of these tests.

Multiple linear regression, used to adjust for age, smoking, and current medical conditions (hypertension, diabetes), were performed in the assessment of associations between test results and exposure groups (contained in Tables 7 through 10). These associations did not change significantly when adjustments for these factors were made. Therefore, only the unadjusted data are presented.

2. October 1989 Medical Survey

a. Participants

Overall, 118 workers participated in the survey. The ten individuals whose urine creatinine was either too low or high to interpret accurately were excluded from the analysis of the renal function tests. Thus, five cadmium-exposed individuals and five non-exposed individuals were excluded from analysis. It is not likely that a bias was introduced by excluding these individuals since there is no demonstrated association between cadmium exposure and abnormal urine creatinine. If for technical reasons, a specific measurement was not obtained, an individual's result was treated as a

missing value.

Based on the cumulative cadmium exposure calculations, participants were reclassified into 3 groups (Table 11). "No exposure" was defined as less than 20 ug-years, which would approximate a 45-year lifetime 8-hour time-weighted average (TWA) exposure of less than 0.5 $ug/m^3$. (Nineteen of 22 workers in this category had a cumulative exposure of 0 ug-years.) "Low exposure" was defined as 20 to 269 ug-years, equivalent to a 45-year TWA exposure of up to 6 $ug/m^3$. "High exposure" was defined as 270 ug-years or greater. The highest cumulative cadmium exposure calculated among participants was 1079 ug-years, which would approximate a 45-year TWA exposure of 24 $ug/m^3$. Of note is the relatively high association between the "a priori" classification of exposure and the cumulative cadmium exposure index (71% concordance).

Participation rates for all 3 groups were similar at approximately 80% (Table 12). In addition, participants in the 3 exposure groups were similar with respect to demographic and other characteristics listed in Table 13 except: 1) the non-exposed smokers had more cigarette pack-years (29.0 vs 11.6 and 15.1; $p=0.02$), and 2) all 3 groups had significantly different levels of urinary cadmium, which increased as the level of cumulative cadmium exposure increased (1.7 vs 6.6 vs 10.4 ug/g creatinine; $p<0.001$). Of note, urinary mean nickel levels were similar for all 3 groups.

b. Urine and Blood Tests

Simple and multiple linear regression analysis were performed to assess the possible associations between renal function tests and cumulative cadmium exposure, while controlling for other factors such as hypertension, diabetes, race, and age. No statistically significant differences in renal function were observed among cumulative cadmium exposure groups, as measured by the tests used in this investigation.

Further analysis compared cadmium-exposed workers with high urine cadmium (greater than or equal to 10 ug/g creatinine) to those with lower values (less than 10 ug/g creatinine) (Table 14). The high urine cadmium group showed higher mean levels of the urinary tubular enzymes NAGA (0.85 vs 0.64 U/g creatinine; $p=0.05$) and AAP (6.14 vs 4.97 U/g creatinine; $p=0.02$), even after adjusting for age, race, hypertension, diabetes, and nickel exposure, as appropriate.

A urine cadmium level above 10 ug/g creatinine has been proposed by OSHA as the level at which medical removal of a worker would be mandatory.[22] In previous studies, 10-15% of the individuals exceeding this level have been estimated to eventually develop renal dysfunction.[30]

In Figure 1, a linear regression model from our data of cadmium-exposed workers showed a significant association ($R^2=0.29$; $p<0.001$) between cumulative cadmium exposure and urine cadmium levels. Using this regression model, an estimated cumulative exposure of 520 ug-years is needed to reach a urine cadmium level of 10 ug/g creat. This cumulative cadmium exposure level would represent, over a 45-year working lifetime, a TWA of approximately 12 $ug/m^3$. Controlling for age, race, and smoking history did not appreciably alter the relationship between urine cadmium and cumulative cadmium exposure. However, it is important to note that, because of the substantial variability in this relationship, this estimate is not precise. Twenty-five percent (18/55) of individuals with cumulative cadmium levels at or below 520 had urine cadmium levels above 10 ug/g creatinine (with a range of 10.3 to 16.9, with 1 value at 28.8 ug/g creatinine).

## VII. CONCLUSIONS

### A. Environmental

Although engineering controls, including local exhaust ventilation systems, have been installed for most of the major operations whose exposures we analyzed, clearly many job categories had mean air concentrations in 1988 which exceeded NIOSH recommendations for cadmium and nickel. Improved engineering controls will be needed in order to meet NIOSH recommended exposure limits. The highest cadmium exposure levels are found in Pressed Plate, while nickel exposures are highest in Plate-making and Plate Preparation.

The inconsistency in the way workstations are designated in the company's database makes computerized analysis difficult. Related jobs are not sorted together by the computer because similar workstations are designated by different names. For example, if all impregnation job stations began with "imp" and if all sintering furnace jobs began with "furn," computerized analysis of data would be enhanced.

### B. Medical

Over-exposure to cadmium was clearly evident in cadmium-exposed workers for both surveys. Nine of 39 (23%) cadmium-exposed workers in the February 1989 medical survey had urine cadmium levels greater than 10 ug/g creatinine. In the October 1989 medical survey, 13 of 47 (28%) workers in the low and 21 of 49 (43%) workers in the high cumulative cadmium exposure groups had urine cadmium levels greater than 10 ug/g creatinine.

No consistent differences in urine proteins were observed between the cadmium-exposed and non-exposed groups in this analysis of either the February or October 1989 medical surveys. In addition, cumulative airborne cadmium levels did not have a significant relationship with any measure of renal function used in our investigation. Possible explanations for this may be due to cumulative cadmium levels having only a 29-34% correlation with urine cadmium levels (Figure 1). The variability between these measures of exposure could have occurred for several reasons:[31]

1. actual work practices may have varied among workers doing identical work - e.g., some workers may have inhaled more airborne cadmium dust than other workers, perhaps due to differences in respirator use;

2. a high respiratory rate could increase pulmonary absorption;

3. variation in rate of metabolism and excretion of cadmium among individual workers.

However, in both surveys, the analysis of cadmium-exposed workers with urine cadmium levels greater than 10 ug/g creatinine (compared to those with less than 10 ug/g creatinine) clearly suggest that the group with higher exposure did have modest elevations of the urinary high-molecular-weight protein albumin, and the low-molecular-weight proteins RBP, NAGA, and AAP, consistent with mild glomerular and tubular dysfunction as reported by others in similarly exposed workers.[30,32] Also, in the February 1989 survey, possible glomerular dysfunction is suggested by a slightly higher mean serum creatinine in the cadmium-exposed group. Considering that the non-exposed group was significantly older, the difference in serum creatinines may actually be larger if the age distributions were equal for both groups.

There is little available published literature about the effects of nickel on the kidney. The mean level of urine nickel in the exposed workers in the February 1989 medical survey was significantly higher than that of the non-exposed workers. However, the mean levels of urine nickel in the low and high cadmium-exposed groups of workers in the October 1989 medical survey were similar to that of the non-exposed group. It would appear that there was little effect of nickel on renal function in our study population. In both the February and October 1989 medical surveys, similar elevations in group means of the urinary high-molecular-weight protein albumin, and the low-molecular-weight proteins RBP, NAGA, and AAP were found from analysis of cadmium-exposed workers with urine cadmium levels greater than 10 ug/g creatinine (compared to those with less than 10 ug/g creatinine).

Several recent studies, using more specific indicators of renal tubular effect, have indicated that subclinical renal dysfunction (elevations of NAGA and AAP) has been observed in cadmium-exposed workers at urine cadmium levels below 10 ug/g creatinine.[33-35] In either of our surveys, abnormal levels of NAGA or AAP (defined by the arithmetic mean in the unexposed plus two standard deviations) were associated only with urine cadmium levels greater than 10 ug/g creatinine.

In the February 1989 medical survey, three of the 39 cadmium-exposed workers (8%) demonstrated evidence of cadmium-induced abnormal renal function using the screening tests (urine albumin, B2M, and RBP) at the end of this report (see section VIII Recommendations). Of these three, two had elevated urine levels of albumin alone, while the other also had elevated urine levels of RBP and B2M. (As noted previously, all elevated levels were defined by the arithmetic mean of the creatinine-standardized measurements in the unexposed plus two standard deviations.) Similar results were found in the October 1989 medical survey. Three of 91 cadmium-exposed workers (3%) had elevated urine levels of albumin, while none had elevated levels of urine RBP. None of the 6 workers described had known non-occupational causes of renal dysfunction (e.g., diabetes, hypertension).

Combining elevated renal function tests from both surveys, four of 41 (10%) cadmium-exposed workers with urine cadmium levels greater than 10 ug/g creatinine demonstrated evidence of cadmium-induced nephropathy. This result is in agreement with the study by Jakubowski, et al.,[30] who estimated that approximately 10% of individuals with urine cadmium levels between 10-15 ug/g will demonstrate evidence of cadmium-related renal disease. Similar conclusions are drawn by Lauwerys, who estimated that 10% of male workers would demonstrate evidence of renal dysfunction at a renal cortex cadmium concentration of 215 ppm.[36] Incidentally, Lauwerys and Roels have found that a cadmium level in the renal cortex of 160 ppm corresponds to a urinary concentration of 10 ug/g creatinine.[4]

Controversy concerning several aspects of cadmium-induced nephropathy still exists. One item of debate is whether increased urinary excretion of high-molecular-weight proteins (such as albumin) occurs as an isolated finding or in association with an increased excretion of low-molecular-weight proteins (such as B2M or RBP). Most studies have indicated that low-molecular-weight proteinuria occurs prior to the development of high-molecular-weight proteinuria. Although our investigation has only six cases of proteinuria, five of six cases (83%) were associated with only increased urinary excretion of albumin. This, as Lauwerys and Bernard have noted, suggests that at least in some individuals, cadmium interferes with glomerular function at an early stage of exposure.[36]

Thus, it appears from our investigation that cadmium-induced renal dysfunction is evident with current available and recommended screening tests in this study population. This investigation also demonstrates that subclinical effects such as increases in mean levels of urinary tubular enzymes NAGA and AAP are apparent in cadmium-exposed workers with urine cadmium levels above 10 ug/g creatinine compared to those below this level.

It is important to note that NIOSH considers cadmium dust and its compounds a potential human carcinogen. Hence, the NIOSH recommended exposure limit (REL) is that employers reduce occupational exposure to cadmium to the lowest feasible limit.[20] Using this approach, cadmium-induced nephropathy should not be an issue.

## VIII. RECOMMENDATIONS

### A. Environmental

1. Exposures to cadmium at the Gates Energy Products, Inc. should be reduced to the fullest extent feasible. Although OSHA is currently proposing a new standard on occupational exposure to cadmium, previous studies demonstrate that the current OSHA PEL of 200 ug/$m^3$ is clearly insufficient to protect workers from renal effects over a 45-year working lifetime.[32, 37] NIOSH has recommended that cadmium be considered a potential human carcinogen and that exposures be reduced to the fullest extent possible.[20]

2. In collecting industrial hygiene sampling data, record related workstation names in a standardized or consistent manner to facilitate computerized analysis. Sorting and statistical analysis for trends would be enhanced.

3. Use the ranked list of workstations, by cadmium and nickel air levels, (provided in this report) to target further engineering control improvements in order to meet recommended exposure limits.

### B. Medical

1. Workers exposed to cadmium should be screened for emphysema and toxic nephropathy (glomerular and tubular types). Screening for emphysema should include a respiratory questionnaire and spirometry. Screening for glomerular nephropathy should include quantitative measurement of urinary albumin; screening for tubular nephropathy should include an assay of urinary low-molecular-weight proteins.[38]

   Thus, the current program of medical surveillance of Gates Energy Products, Inc. workers at the Gainesville plant should be expanded to include measurement of the above mentioned tests. Simultaneous measurement of urine creatinine with quantitative measurements of urinary albumin and low-molecular-weight proteins is encouraged in order to creatinine-standardize the urine tests to adjust for variations in urine concentration. Although urinary beta-2-microglobulin (B2M) testing is the most widely available and more thoroughly studied indicator of early cadmium tubular nephropathy, B2M degrades in acid urine. Urinary retinol binding protein (RBP) should be substituted for B2M once it has become more widely available as a screening test assay.

2. Cadmium-induced renal disease appears to be progressive and irreversible.[32, 39] Medical removal is appropriate for employees with proteinuria and in most cases the worker would be ill-advised to return to a job involving cadmium exposure.

   The following action plan has been proposed by NIOSH for dealing with elevated urinary low-molecular-weight protein levels:

   a. All abnormal results should be repeated to confirm the results. (There are no meaningful "normal" values established for urinary low-molecular-weight proteins; a result more than two standard deviations above the laboratory's mean should be considered "elevated" for medical screening purposes.)

   b. If re-testing confirms an abnormal result, the employee should be informed of the test result and referred for a clinical evaluation to assess renal function and to explore other potential nonoccupational etiologies of low-molecular-weight proteinuria.

   c. If clinical evaluation determines renal function to be normal and other causes of low-molecular-weight proteinuria are excluded, the workers should be notified of this assessment; the worker should be retested at 3 month intervals. An industrial hygiene survey should be undertaken to assess and control potential exposures.

   d. Although no data document when a worker should be removed from further exposure, a reasonable approach would be to remove any worker from exposure to cadmium who is found to have any of the following:

(1) two separate screening results (i.e., not including confirmatory retesting described above) that exceed the upper limit of normal, or

(2) progressive increases in low-molecular-weight proteinuria over time, or

(3) documented renal disease on further clinical evaluation.

e. Any worker removed from exposure to cadmium as a result of low-molecular-weight proteinuria (see d above), who is not found to have another probable etiology should be reported as a case of toxin-induced nephropathy.

A similar decision logic can also be applied for evaluating an abnormal quantitative measurement of urinary albumin which should be used as a screening test for glomerular nephropathy (see 2 above).

NIOSH does not recommend the use of medical removal as a substitution for other more effective methods of protecting workers (primary prevention). However, in cases where medical removal is necessary (as described above), the wages and benefits of such employees should be protected.[40]

## IX. REFERENCES


1. Hornung RW and Reed LD: Estimation of average concentration in the presence of nondetectable values. Appl Occup Environ Hyg 5(1): 46-51, 1990.

2. Freiburg L, et al: Handbook on the Toxicology of Metals. Vol II; Specific Metals: Amsterdam: Elsevier Press p. 140, 1986.

3. Webb M: Cadmium. Br Med Bull 31: 246-50, 1975.

4. Lauwerys RR: Industrial Chemical Exposure: Guidelines for Biological Monitoring. Davis, CA: Biomedical Publications, pp. 17-24, 1983.

5. Lauwerys R, Roels H, et al: Significance of cadmium concentration in blood and in urine in workers exposed to cadmium. Envir Res 20: 375-91, 1979.

6. Kjellstrom T: Exposure and accumulation of cadmium in populations from Japan, the United States, and Sweden. Environ Health Perspect 28: 169-97, 1979.

7. Ellis KJ, Vartsky D, et al: Cadmium: in vivo measurement in smokers and non-smokers. Science 205: 323-25, 1979.

8. Agency for Toxic Substances and Disease Registry. Toxicological profile for cadmium. DHHS (ATSDR) Publication No. 88-08, March 1989.

9. Freiburg L, et al: Cadmium in the Environment. Cleveland: CRC Press, 1974.

10. Baker EL, et al: Subacute cadmium intoxication in jewelry workers: An evaluation of diagnostic procedures. Arch Env Health 34: 173-77, 1979.

11. Scott R, et al: Clinical and biochemical abnormalities in coppersmiths exposed to cadmium. Lancet 2: 396-98, 1976.

12. Discutor M: Role of cadmium in carcinogenesis with special reference to cancer of the prostate. Environ Health Perspect 40: 107-20, 1981.

13. Lemen R, et al: Cancer mortality survey of workers exposed to cadmium. Ann NY Acad Sci 271: 273-79, 1976.

14. International Agency for Research on Cancer. Monograph on the Evaluation of carcinogenic risk of chemicals to non-cadmium and cadmium compounds. 11: 39-74, 1976.

15. Kido T, et al: Progress of renal dysfunction in inhabitants environmentally exposed to cadmium. Arch Env Health 43: 313-217, 1988.

16. Page LB and Culver PJ: A Syllabus of Laboratory Examinations in Clinical Diagnosis. Cambridge: Harvard University Press, 1962.

17. National Institute for Occupational Safety and Health. Criteria for a Recommended Standard....Occupational Exposure to Cadmium. DHEW (NIOSH) Publication No. 76-192, August 1976.

18. American Conference Governmental Industrial Hygienist: Documentation of the Threshold Limit Values and Biological Exposure Indices, 5th ed. Cincinnati, Ohio: ACGIH, 1986.

19. World Health Organization Study Group: Recommended health based limits in occupational exposures to heavy metals. Tech Rep Ser Wld Hlth Org, 647: 21-35, 1980.

20. National Institute for Occupational Safety and Health. Current Intelligence Bulletin 42: Cadmium. DHHS (NIOSH) Publication No. 84-116, September 27, 1984.

21. American Conference of Governmental Industrial Hygienists: Threshold Limit Values for Chemical Substances in the Work Environment Adopted by ACGIH with Intended Changes for 1989-90. Cincinnati, Ohio: ACGIH 1988-89 TLV booklet.

22. Federal Register, Department of Labor, Occupational Safety and Health Administration, 29 CFR Part 1910: Proposed Rules: Occupational Exposure to Cadmium. 55 (25): 4052-4147, February 6, 1990.

23. Proctor N, et al: Chemical Hazards of the Workplace, 2nd edition, Philadelphia: J.B. Lippincott Company, 1988.

24. Tsalev DL and Zaprianov ZK: Analytic Aspects and Health Significance, In: Atomic Absorption Spectrometry in Occupational and Environment Health Practice, Vol. 1, Boca Raton, Fla.: CRC Press, p. 175, 1983.

25. Mastromatteo E: Nickel. Amer Ind Hyg Assoc J 47: 589-601, 1986

26. National Institute for Occupational Safety and Health (NIOSH): HETA 84-288-1847, Wheel Trueing Tool Company, Columbia, South Carolina, 1987.

27. Gitlitz PH, et al: Aminoaciduria and proteinuria in rats after a single intraperitoneal injection of Ni(II). Tox Appl Pharmacol 34: 430-448, 1975.

28. National Institute for Occupational Safety and Health. Criteria for a Recommended Standard....Occupational Exposure to Inorganic Nickel. DHEW (NIOSH) Publication No. 77-164, May 1977.

29. American Conference of Governmental Industrial Hygienists: Threshold Limit Values for Chemical Substances in the Work Environment Adopted by ACGIH with Intended Changes for 1990-91. Cincinnati, Ohio: ACGIH 1989-90 TLV booklet.

30. Jakubowski M, et al: Occupational exposure to cadmium and kidney dysfunction. Int Arch Occ Env Health 59: 567-77, 1987.

31. Rempel DM, Rosenberg J, Harrison RJ: Biological monitoring. Chapter 34, pp 459-466, In: Occupational Medicine, 1st edition. Appleton and Lange, 1990.

32. Thun MJ, Osorio AM, et al: Nephropathy in cadmium workers: assessment of risk from airborne occupational exposure to cadmium. Brit J Ind Med 46: 689-697, 1989.

33. Mueller PW, Smith SJ, et al: Chronic tubular effects in relation to urine cadmium levels. Nephron 52: 45-54, 1989.

34. Kawada T, Koyama H, Suzuki S: Cadmium, NAG activity, and B2-microglobulin in the urine of cadmium pigment workers. Br J Ind Med 46:52-55, 1989.

35. Chia KS et al: Renal tubular function of workers exposed to low levels of cadmium. Brit J Ind Med 46: 165-170, 1989.

36. Lauwerys RR and Bernard AM: Cadmium and the kidney (editorial). Brit J Ind Med 43: 433-435, 1986.

37. Falck FY et al: Occupational cadmium exposure and renal status. Am J Ind Med 4: 541-549, 1983.

38. Roels HA, Lauwerys RR, et al: Health significance of cadmium induced renal dysfunction: a five year follow up. Brit J Ind Med 46: 755-764, 1989.

39. National Institute for Occupational Safety and Health. Comments of the National Institute for Occupational Safety and Health on the Occupational Safety and Health Administration's proposed rule on occupational exposure to cadmium. DHHS (NIOSH) Docket No. H-057a, June 1990.

40. National Institute for Occupational Safety and Health. Comments of the National Institute for Occupational Safety and Health on the Occupational Safety and Health Administration's advance notice of proposed rulemaking on generic standard for medical surveillance programs for employees (29 CFR 1910: Docket No. H-031), December 20, 1988. NIOSH Policy Statements, Cincinnati, Ohio: U.S. Department of Health and Human Services. Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health.

41. Tietz N: Clinical Guide to Laboratory Tests. Sanders, pp. 430-31, 1983.

42. Sunderman FW: Analytical biochemistry of nickel. Pure Appl Chem 52: 527-544, 1980.

## X. AUTHORSHIP AND ACKNOWLEDGEMENTS


Report prepared by:

Richard R. Hammel, M.D., M.P.H.
Medical Officer
Medical Section

Stephen L. Klincewicz, D.O.
Medical Officer
Medical Section

Anne T. Fidler, Sc.D.
Supervisory Epidemiologist
Medical Section

Paul Roper, CIH
Industrial Hygienist
Industrial Hygiene Section
Hazard Evaluations and Technical
Assistance Branch

Alice L. Greife, Ph.D.
Senior Scientist
Industrial Hygiene Section
Industrywide Studies Branch

Originating office:

Hazard Evaluations and Technical
Assistance Branch
Division of Surveillance, Hazard
Evaluations, and Field Studies



The authors would like to acknowledge the following NIOSH personnel: Kathy Watkins, for assisting in preparation of questionnaires; Don Bates, for supervising data entry; Rick Driscoll and David Orgel, for administering questionnaires and assisting in collection of measurements; and Raymond Biagini and Gerry Henningsen for providing immunologic laboratory analysis.

In addition, the authors would like to thank the following Center for Environmental Health personnel: Brenda Lewis and Charles Dodson, for assisting in specimen collection and preparation; and Patricia Mueller, for coordinating and supervising laboratory analysis.

Finally, the investigations would not have been possible without the cooperation of the management and employees of Gates Energy Products, Inc.


## XI. DISTRIBUTION AND AVAILABILITY

Copies of this report are temporarily available upon request from NIOSH, Hazard Evaluations and Technical Assistance Branch, 4676 Columbia Parkway, Cincinnati, Ohio 45226. After 90 days, the report will be available through the National Technical Information Service (NTIS), 5285 Port Royal, Springfield, Virginia 22161. Information regarding its availability through NTIS can be obtained from the NIOSH Publications Office at the Cincinnati address. Copies of this report have been sent to:

1. OSHA Region IV
2. International Brotherhood of Electrical Workers (IBEW), Local 2156, Gainesville, Florida
3. Gates Energy Products, Inc., Gainesville, Florida
4. NIOSH Atlanta Region

For the purpose of informing affected employees, copies of this report should be posted by Gates Energy Products, Inc. in a prominent place that is accessible to employees for a period of 30 calendar days.

TABLE 1

1988 Cadmium Exposure Levels, By Work Area

Gates Energy Products, Inc.
Gainesville, Florida
HETA 88-199

Concentrations Expressed As ug/m$^{3*}$

| Area and Operation | Mean | Median | Standard Deviation | Range | No. of Samples |
|---|---|---|---|---|---|
| Plate-making Department | | | | | |
| Nickel plating | 6 | 1 | 9.3 | 1 - 31 | 12 |
| Nickel slurry preparation | 3 | 1 | 4.2 | 1 - 14 | 9 |
| Sintering furnaces | 6 | 3 | 8.6 | 1 - 41 | 23 |
| Sizing | 8 | 6 | 7.9 | 1 - 19 | 4 |
| Spiralling | 5 | 6 | 2.5 | 3 - 9 | 5 |
| Impregnation | 9 | 7 | 8.8 | 1 - 42 | 22 |
| Despiralling | 68 | 58 | 49 | 10 - 144 | 6 |
| Electrochemical cleaning | 31 | 15 | 37 | 1 - 130 | 14 |
| Maintenance jobs | 15 | 13 | 13 | 1 - 53 | 40 |

* ug/m$^3$: micrograms of cadmium per cubic meter of air, calculated as a time-weighted average for the work shift

TABLE 1 (Continued)

1988 Cadmium Exposure Levels, By Work Area

Gates Energy Products, Inc.
Gainesville, Florida
HETA 88-199

Concentrations Expressed As $ug/m^{3*}$

| Area and Operation | Mean | Median | Standard Deviation | Range | No. of Samples |
|---|---|---|---|---|---|
| Pressed Plate Department | | | | | |
| Preparation of paste | 367 | 185 | 496 | 18 - 1914 | 23 |
| Tab welding | 35 | 35 | 4 | 31 - 44 | 6 |
| Paste machine operation | 113 | 86 | 97 | 18 - 716 | 119 |
| Tab staking | 74 | 72 | 35 | 19 - 180 | 36 |
| Slitting | 31 | 25 | 14 | 13 - 47 | 7 |
| Setting up process/machines | 111 | 114 | 13 | 93 - 124 | 4 |
| Maintenance jobs | 61 | 39 | 77 | 2 - 373 | 22 |
| Materials handling | 48 | 41 | 36 | 8 - 113 | 8 |
| Dipping paste | 195 | 195 | 0 | ----- | 1 |
| Rovers (job to job) | 66 | 56 | 34 | 16 - 123 | 8 |
| Leaders (crew chiefs) | 67 | 53 | 55 | 14 - 196 | 8 |
| Rework/reclaim/shaker | 95 | 89 | 48 | 33 - 198 | 17 |

* $ug/m^3$: micrograms of cadmium per cubic meter of air, calculated as a time-weighted average for the work shift

TABLE 1 (Continued)

1988 Cadmium Exposure Levels, By Work Area

Gates Energy Products, Inc.
Gainesville, Florida
HETA 88-199

Concentrations Expressed As $ug/m^{3*}$

| Area and Operation | Mean | Median | Standard Deviation | Range | No. of Samples |
|---|---|---|---|---|---|
| Plate Preparation Department | | | | | |
| Slitting and blanking | 20 | 13 | 29 | 1 - 129 | 27 |
| Sorting and stacking | 21 | 12 | 23 | 6 - 98 | 18 |
| Materials handling | 14 | 9 | 11 | 7 - 27 | 3 |
| rework (reclamation) | 16 | 8 | 16 | 4 - 43 | 6 |
| Winding and Closing Department | | | | | |
| Winding cells | 21 | 12 | 21 | 4 - 70 | 17 |
| Closing cells | 5 | 2 | 6 | 1 - 21 | 15 |

* $ug/m^3$: micrograms of cadmium per cubic meter of air, calculated as a time-weighted average for the work shift

TABLE 2

Jobs Ranked By Mean Cadmium Concentration for 1988

Gates Energy Products, Inc.
Gainesville, Florida
HETA 88-199

| Job or Operation | Area | Mean Cd Concentration ($ug/m^3$)* |
|---|---|---|
| Preparation of paste | Pressed Plate | 367 |
| Dipping paste | Pressed Plate | 195 |
| Paste machine operation | Pressed Plate | 113 |
| Setting up process/machinery | Pressed Plate | 111 |
| Rework/reclaim/shaker | Pressed Plate | 95 |
| Tab staking | Pressed Plate | 74 |
| Despiralling | Plate-making | 68 |
| Leaders (crew chiefs) | Pressed Plate | 67 |
| Rovers (job to job) | Pressed Plate | 66 |
| Maintenance jobs | Pressed Plate | 61 |
| Materials handling | Pressed Plate | 48 |
| Tab welding | Pressed Plate | 35 |
| Slitting | Pressed Plate | 31 |
| Electrochemical cleaning | Plate-making | 31 |
| Sorting and stacking | Plate Preparation | 21 |
| Winding cells | Winding and closing | 21 |
| Slitting and blanking | Plate Preparation | 20 |
| Rework (reclamation) | Plate Preparation | 16 |
| Maintenance jobs | Plate-making | 15 |
| Materials handling | Plate Preparation | 14 |
| Impregnation | Plate-making | 9 |
| Sizing | Plate-making | 8 |
| Sintering furnaces | Plate-making | 6 |
| Nickel plating | Plate-making | 6 |
| Spiralling | Plate-making | 5 |
| Closing cells | Winding and Closing | 5 |
| Nickel slurry preparation | Plate-making | 3 |

* $ug/m^3$: micrograms of cadmium per cubic meter of air, calculated as a time-weighted average for the work shift

TABLE 3

1988 Nickel Exposure Levels, By Work Area

Gates Energy Products, Inc.
Gainesville, Florida
HETA 88-199

| Area and Operation | Concentrations Expressed As ug/m³* Mean | Median | Standard Deviation | Range | No. of Samples |
|---|---|---|---|---|---|
| Plate-making Department | | | | | |
| Nickel plating | 18 | 13 | 11 | 7 - 38 | 12 |
| Nickel slurry preparation | 496 | 440 | 338 | 187 - 1199 | 9 |
| Sintering furnaces | 151 | 38 | 435 | 11 - 2126 | 23 |
| Sizing | 16 | 12 | 8 | 11 - 27 | 4 |
| Spiralling | 40 | 55 | 28 | 10 - 67 | 5 |
| Impregnation | 20 | 16 | 12 | 4 - 56 | 22 |
| Despiralling | 36 | 28 | 22 | 8 - 69 | 6 |
| Electrochemical cleaning | 32 | 24 | 22 | 6 - 79 | 14 |
| Maintenance jobs | 17 | 8 | 23 | 3 - 92 | 40 |

* ug/m³: micrograms of cadmium per cubic meter of air, calculated as a time-weighted average for the work shift

TABLE 3 (Continued)

1988 Nickel Exposure Levels, By Work Area

Gates Energy Products, Inc.
Gainesville, Florida
HETA 88-199

Concentrations Expressed As ug/m$^{3*}$

| Area and Operation | Mean | Median | Standard Deviation | Range | No. of Samples |
|---|---|---|---|---|---|
| Pressed Plate Department | | | | | |
| Preparation of paste | 44 | 8 | 59 | 1 - 170 | 14 |
| Tab welding | 11 | 11 | 0.6 | 11 - 12 | 3 |
| Paste machine operation | 2 | 2 | 1 | 0 - 4 | 56 |
| Tab staking | 2 | 3 | 1 | 1 - 3 | 18 |
| Slitting | 22 | 22 | 13 | 12 - 31 | 2 |
| Setting up process/machines | 3 | 3 | 0 | 3 - 3 | 3 |
| Maintenance jobs | 4 | 3 | 2 | 1 - 11 | 15 |
| Materials handling | 13 | 15 | 11 | 2 - 23 | 3 |
| Rovers (job to job) | 8 | 3 | 10 | 3 - 24 | 4 |
| Leaders (crew chiefs) | 3 | 3 | 1 | 1 - 4 | 5 |
| Rework/reclaim/shaker | 7 | 6 | 4 | 1 - 14 | 16 |

* ug/m$^3$: micrograms of cadmium per cubic meter of air, calculated as a time-weighted average for the work shift

TABLE 3 (Continued)
1988 Nickel Exposure Levels, By Work Area

Gates Energy Products, Inc.
Gainesville, Florida
HETA 88-199

| Area and Operation | Concentrations Expressed As ug/m$^3$* Mean | Median | Standard Deviation | Range | No. of Samples |
|---|---|---|---|---|---|
| Plate Preparation Department | | | | | |
| Slitting and blanking | 53 | 42 | 46 | 8 - 241 | 27 |
| Sorting and stacking | 37 | 33 | 30 | 6 - 111 | 18 |
| Materials handling | 118 | 34 | 168 | 9 - 312 | 3 |
| rework (reclamation) | 30 | 28 | 12 | 17 - 48 | 6 |
| Winding and Closing Department | | | | | |
| Winding cells | 20 | 8 | 30 | 1 - 105 | 17 |
| Closing cells | 4 | 2 | 9 | 1 - 35 | 15 |

* ug/m$^3$: micrograms of cadmium per cubic meter of air, calculated as a time-weighted average for the work shift

TABLE 4

Jobs Ranked By Mean Nickel Concentration for 1988

Gates Energy Products, Inc.
Gainesville, Florida
HETA 88-199

| Job or Operation | Area | Mean Ni Concentration ($ug/m^3$)* |
|---|---|---|
| Nickel slurry preparation | Plate-making | 496 |
| Sintering furnaces | Plate-making | 151 |
| Materials handling | Plate Preparation | 118 |
| Slitting and blanking | Plate Preparation | 53 |
| Preparation of paste | Pressed Plate | 44 |
| Spiralling | Plate-making | 40 |
| Sorting and stacking | Plate Preparation | 37 |
| Despiralling | Plate-making | 36 |
| Electrochemical cleaning | Plate-making | 32 |
| Rework (reclamation) | Plate Preparation | 30 |
| Slitting | Pressed Plate | 22 |
| Impregnation | Plate-making | 20 |
| Winding cells | Winding and Closing | 20 |
| Nickel plating | Plate-making | 18 |
| Maintenance jobs | Plate-making | 17 |
| Sizing | Plate-making | 16 |
| Materials handling | Pressed Plate | 13 |
| Tab welding | Pressed Plate | 11 |
| Rovers (job to job) | Pressed Plate | 8 |
| Rework/reclaim/shaker | Pressed Plate | 7 |
| Maintenance jobs | Pressed Plate | 4 |
| Closing cells | Winding and Closing | 4 |
| Leaders (crew chiefs) | Pressed Plate | 3 |
| Setting up process/machinery | Pressed Plate | 3 |
| Tab staking | Pressed Plate | 2 |
| Paste machine operation | Pressed Plate | 2 |

* $ug/m^3$: micrograms of cadmium per cubic meter of air, calculated as a time-weighted average for the work shift

TABLE 5

Characteristics of Study Participants

Gates Energy Products, Inc.
Gainesville, Florida
HETA 88-199

February 1989

| Variable | Exposed | Unexposed | p value[1] |
|---|---|---|---|
| Number | 39 | 36 | |
| Age | 42.0 (7.4)[2] | 49.9 (7.9) | 0.001 |
| Race (% white) | 17/34 (50%) | 32/36 (89%) | 0.001 |
| % Ever Smoked | 19 (49%) | 23 (64%) | 0.19 |
| % Current Smokers | 11/39 (28%) | 8/31 (26%) | 0.56 |
| Mean pack years | 9.1 (10.0) | 20.2 (15.5) | 0.008 |
| Mean Systolic B.P. | 134.5 (15.9) | 130.2 (11.7) | 0.20 |
| Mean diastolic B.P. | 85.2 (9.0) | 85.7 (8.2) | 0.81 |
| Height (inches) | 69.6 (3.4) | 70.9 (2.9) | 0.38 |
| % Hypertensives | 8/36 (22%) | 7/36 (19%) | 0.77 |
| Aspirin Use[3] | 9 (23%) | 10 (28%) | 0.84 |
| Cadmium (ug/g creat) | 5.99 (4.9) | 0.8 (0.5) | 0.001 |
| Nickel (ug/g creat) | 7.4 (6.4) | 1.6 (0.8) | 0.001 |

1 - t-test for continuous variables; chi-square or Fisher's exact test (2-tailed) for categorical variables (A p value less than or equal to 0.05 is considered to represent a "statistically significant" difference between the exposed and unexposed groups.)

2 - Arithmetic mean and (standard deviation)

3 - "Have you ever used headache, arthritis, or pain pills such as Aspirin, Tylenol, Advil, or Motrin for a total amount of time of 6 months or more?"

EXPOSED WORKERS

| Variable | Urine Cadmium 10 + ug/g creat | Urine Cadmium < 10 ug/g creat | p value[2] |
|---|---|---|---|
| Number | 9 | 30 | |
| Age | 44.3 | 41.3 | 0.29 |
| Race (% white) | 2 (29%) | 15 (57%) | 0.40 |
| % ever smoked | 7/9 (78%) | 12/30 (40%) | 0.06 |
| Current Smokers | 6/9 (67%) | 5/25 (20%) | 0.02 |
| Mean pack years | 14.1 (12.5) | 9.3 (7.9) | 0.35 |
| Mean systolic B.P. | 139.8 (12.3) | 132.9 (16.7) | 0.26 |
| Mean diastolic B.P. | 86.9 (11.1) | 84.7 (8.4) | 0.52 |
| Height (inches) | 69.8 (3.8) | 69.6 (3.3) | 0.87 |
| Weight (pounds) | 174.2 (33.8) | 197.7 (34.7) | 0.08 |
| % Hypertensives | 1/6 (17%) | 7/30 (23%) | 0.72 |

TABLE 6

Reported medical conditions and previous exposure history

Gates Energy Products, Inc.
Gainesville, Florida
HETA 88-199

February 1989

| Medical Condition | Exposed | Unexposed | R.R. (C.I.)* |
|---|---|---|---|
| Any Kidney Condition | 0 | 1 (3%) | |
| Any Lung Condition | 1 (3%) | 1 (3%) | 1.0 (0.07, 15.8) |
| Diabetes | 1 (3%) | 1 (3%) | 1.0 (0.07, 15.8) |
| Prostate Disease | 1 (3%) | 5 (14%) | 0.2 (0.03, 1.7) |
| Kidney Stones | 2 (5%) | 5 (14%) | 0.4 (0.07, 1.7) |
| Blood in Urine | 1 (3%) | 4 (11%) | 0.2 (0.03, 2.0) |
| Protein in Urine | 0 | 0 | |
| Gout | 1 (3%) | 1 (3%) | 0.9 (0.06, 14.2) |
| Immune Disease | 1 (3%) | 0 | |
| Anemia | 0 | 1 (3%) | |
| **Prior Exposure** | | | |
| Cadmium | 5 (14%) | 3 (9%) | 1.6 (0.4, 6.1) |
| Lead | 2 (6%) | 2 (6%) | 1.0 (0.1, 6.7) |
| Nickel | 4 (11%) | 3 (9%) | 1.3 (0.3, 5.4) |
| Mercury | 0 | 2 (6%) | |
| Other Metals | 3 (8%) | 6 (17%) | 0.5 (0.1, 1.7) |
| Solvents | 4 (11%) | 9 (26%) | 0.4 (0.1, 1.3) |

* R.R.: Relative Risk (rate in exposed/rate in unexposed)
C.I.: 95% Confidence Interval

TABLE 7

ARITHMETIC MEAN VALUES
EXPOSED vs NON-EXPOSED

Gates Energy Products, Inc.
Gainesville, Florida
HETA 88-199

February 1989

| Urine Analyte | Exposed | Unexposed | p Value[1] |
|---|---|---|---|
| Number | 39 | 36 | |
| Albumin (mg/g creat) | 4.3 (6.6)[2] | 2.7 (.15) | 0.15 |
| Creatinine (mg/dL) | 186.9 (66.6) | 177.9 (71.4) | 0.57 |
| NAGA (U/g creat) | 0.8 (0.6) | 1.0 (0.9) | 0.25 |
| AAP (U/g creat) | 4.7 (3.1) | 5.5 (2.1) | 0.19 |
| GGT (U/g creat) | 14.6 (3.9) | 20.0 (6.1) | 0.001 |
| RBP (mg/g creat) | 0.08 (0.06) | 0.11 (0.07) | 0.02 |
| B2M (ug/g creat) | 98.3 (123.1) | 108.8 (177.5) | 0.77 |
| Phosphorous (mg/g creat) | 48.1 (19.0) | 51.3 (18.0) | 0.45 |
| **Serum analyte** | | | |
| Albumin (g/L) | 4.2 (0.2) | 4.3 (0.2) | 0.001 |
| Creatinine (mg/dL) | 1.2 (0.3) | 1.0 (0.1) | 0.001 |
| Phosphorous (mg/dL) | 3.9 (0.4) | 3.7 (0.4) | 0.07 |
| RBP (mg/dL) | 4.7 (0.8) | 5.2 (1.5) | 0.10 |

1 - t-test (A p value less than or equal to 0.05 is considered to represent a "statistically significant" difference between the exposed and unexposed groups.)

2 - Mean and (standard deviation)

TABLE 8

ARITHMETIC MEAN VALUES
CADMIUM GROUPS: HIGH vs LOW

Gates Energy Products, Inc.
Gainesville, Florida
HETA 88-199

February 1989

| Urine Analyte | Urine Cadmium 10 + ug/g creat | Urine Cadmium < 10 ug/g creat | p value[1] |
|---|---|---|---|
| Number | 9 | 30 | |
| Albumin (mg/g creat) | 7.7 (9.5)[2] | 2.9 (3.5) | 0.17 |
| Creatinine (mg/dL) | 167.1 (53.5) | 196.3 (70.8) | 0.26 |
| NAGA (U/g creat) | 1.0 (0.5) | 0.6 (0.4) | 0.03 |
| AAP (U/g creat) | 6.9 (4.9) | 4.0 (2.0) | 0.11 |
| GGT (U/g creat) | 15.6 (4.8) | 14.3 (3.6) | 0.39 |
| RBP (mg/g creat) | 0.12 (0.10) | 0.065 (0.04) | 0.16 |
| B2M (ug/g creat) | 189.6 (244.2) | 73.1 (39.3) | 0.22 |
| Phosphorous (mg/g creat) | 45.3 (15.8) | 49.0 (20.1) | 0.60 |
| TRP % | 85.7 (4.5) | 84.9 (6.4) | 0.74 |
| Nickel (ug/g creat) | 9.3 (10.0) | 6.6 (4.1) | 0.44 |
| **Serum analyte** | | | |
| Albumin (g/dL) | 4.0 (0.1) | 4.2 (0.2) | 0.002 |
| Creatinine (mg/dL) | 1.2 (0.1) | 1.2 (0.3) | 0.89 |
| Phosphorous (mg/dL) | 3.9 (0.4) | 3.8 (0.4) | 0.68 |
| RBP (mg/dL) | 4.8 (0.8) | 4.7 (0.8) | 0.72 |

1 - t-test (A p value less than or equal to 0.05 is considered to represent a "statistically significant" difference between the exposed and unexposed groups.)

2 - Mean and (standard deviation)

TABLE 9

Hematologic and immunologic test results
ARITHMETIC MEAN VALUES
EXPOSED vs UNEXPOSED

Gates Energy Corporation
Gainesville, Florida
HETA 88-199

February 1989

| Analyte | Exposed | Unexposed | p Value[1] |
|---|---|---|---|
| Number | 39 | 36 | |
| CD3 (Total T cell %) | 68.9 (11.3)[2] | 71.2 (8.3) | 0.31 |
| CD4 (% Helper) | 44.2 (7.3) | 47.0 (7.1) | 0.09 |
| CD8 (% Suppressors) | 29.2 (8.0) | 26.7 (7.2) | 0.16 |
| H/S Ratio | 1.7 (0.7) | 1.9 (0.7) | 0.13 |
| CD20 (Total B-cells %) | 4.6 (3.4) | 4.3 (2.3) | 0.65 |
| NKH1 (Natural Killer %) | 4.2 (3.2) | 5.3 (3.5) | 0.21 |
| IgA (mg/dL) | 221.0 (77.0) | 205.5 (80.0) | 0.40 |
| IgG (mg/dL) | 1231.4 (358.1) | 1035.9 (184.7) | 0.004 |
| IgM (mg/dL) | 119.8 (51.4) | 121.9 (83.3) | 0.90 |
| NK Activity 25 | 21.3 (12.5) | 23.6 (19.8) | 0.55 |
| NK Activity 50 | 37.0 (21.3) | 33.4 (21.5) | 0.49 |
| WBC (thous/$mm^3$) | 6.1 (1.9) | 6.1 (1.7) | 0.91 |
| Lymphocytes (%) | 37.9 (8.9) | 34.5 (6.8) | 0.07 |
| RBC (mil/$mm^3$) | 4.9 (0.4) | 4.9 (0.3) | 0.52 |
| Hemoglobin (gm/dL) | 14.8 (0.8) | 15.2 (0.8) | 0.03 |
| Hematocrit (%) | 43.2 (2.1) | 44.0 (2.3) | 0.09 |
| MCV (fl) | 89.1 (5.0) | 89.7 (5.6) | 0.64 |
| MCHC (gm/dl) | 34.3 (0.7) | 34.6 (0.7) | 0.03 |
| MCH (pg) | 30.6 (2.0) | 31.1 (2.3) | 0.34 |
| Platelets (thous/$mm^3$) | 295.5 (62.5) | 273.5 (59.1) | 0.12 |

1 - t-test (A p value less than or equal to 0.05 is considered to represent a "statistically significant" difference between the exposed and unexposed groups.)

2 - Mean and (standard deviation)

TABLE 10

Hematologic and immunologic test results
EXPOSED ONLY

Gates Energy Products, Inc.
Gainesville, Florida
HETA 88-199

February 1989

Urine Cadmium

| Analyte | 10+ ug/g creat | < 10 ug/g creat | p value[1] |
|---|---|---|---|
| Number | 9 | 29 | |
| CD3 (Total T %) | 68.4 (10.4)[2] | 69.2 (11.6) | 0.88 |
| CD4 (% Helpers) | 43.9 (7.3) | 44.2 (7.1) | 0.91 |
| CD8 (% Suppressors) | 30.3 (6.6) | 28.8 (8.4) | 0.63 |
| H/S Ratio | 1.58 (0.7) | 1.7 (0.7) | 0.64 |
| NKH1 (% N K) | 4.94 (5.1) | 3.9 (3.5) | 0.49 |
| IgA (mg/dL) | 194.60 (84.2) | 229.3 (74.3) | 0.24 |
| IgG (mg/dL) | 1292.78 (309.1) | 1254.8 (301.3) | 0.75 |
| IgM (mg/dL) | 93.11 (19.8) | 128.1 (55.5) | 0.07 |
| NK Activity 25 | 20.34 (14.5) | 21.5 (12.1) | 0.81 |
| NK Activity 50 | 38.63 (23.2) | 36.5 (21.1) | 0.81 |
| WBC (thous/$mm^3$) | 6.11 (1.8) | 6.1 (2.0) | 0.95 |
| Lymphocytes (%) | 34.24 (12.0) | 39.0 (6.8) | 0.29 |
| RBC (mil/$mm^3$) | 4.72 (0.3) | 4.9 (0.4) | 0.16 |
| Hemoglobin (gm/dL) | 14.6 (0.9) | 14.9 (0.7) | 0.26 |
| Hematocrit (%) | 42.2 (2.1) | 43.4 (2.1) | 0.11 |
| MCV (fl) | 90.21 (2.9) | 88.8 (5.4) | 0.47 |
| MCHC (gm/dl) | 34.02 (1.1) | 34.3 (0.5) | 0.25 |
| MCH (pg) | 30.97 (1.4) | 30.5 (2.2) | 0.57 |
| Platelets (thous/$mm^3$) | 308.33 (89.0) | 291.7 (53.5) | 0.61 |

1 - t-test (A p value less than or equal to 0.05 is considered to represent a "statistically significant" difference between the exposed and unexposed groups.)

2 - Mean and (standard deviation).

TABLE 11

Comparison of Cadmium Exposure Categorizations

Gates Energy Products, Inc.
Gainesville, Florida
HETA 88-199

October 1989

| Cumulative Exposure | ----------A Priori Classification ---------- None | Low | High | Total |
|---|---|---|---|---|
| None | 22 | 0 | 0 | 22 |
| Low | 11 | 29 | 7 | 47 |
| High | 0 | 16 | 33 | 49 |
| | 33 | 45 | 40 | 118 |

% Concordance = 71%

TABLE 12

Study participation rates

Gates Energy Products, Inc.
Gainesville, Florida
HETA 88-199

October 1989

| A Priori | # Eligible | # Participated | % Participation |
|---|---|---|---|
| None | 42 | 33 | 79% |
| Low | 56 | 45 | 80% |
| High | 50 | 40 | 80% |

TABLE 13

Characteristics of study participants

Gates Energy Products, Inc.
Gainesville, Florida
HETA 88-199

October 1989

Cadmium Exposure Category

| Variable | NONE | LOW | HIGH | p value[1] |
|---|---|---|---|---|
| Number | 22 | 47 | 49 | |
| Age | 45.9 (8.1)[2] | 45.6 (7.9) | 44.8 (7.0) | 0.82 |
| Race (% white) | 77% | 60% | 59% | 0.30 |
| % Ever Smoked | 41% | 36% | 3l% | 0.78 |
| Mean pack years (smokers only) | 29.0 (21.7) | 11.6 (9.4) | 15.1 (12.8) | 0.02 |
| % Hypertensives | 9% | 26% | 14% | 0.18 |
| % Diabetic | 5% | 4% | 8% | 0.69 |
| Cadmium (ug/g creat) | 1.7 (1.6) | 6.6 (6.0) | 10.4 (7.0) | <0.001 |
| Nickel (ug/g creat) | 3.1 (2.2) | 4.3 (3.9) | 3.1 (2.0) | 0.12 |

1 - Analysis of variance for continuous variable; chi-square for categorical variables (A p value less than or equal to 0.05 is considered to represent a "statistically significant" difference between the exposed and unexposed groups.)

2 - Arithmetic mean and (standard deviation).

TABLE 14

Adjusted [1] Means: Renal Function Tests
Among Cadmium-exposed

Gates Energy Products, Inc.
Gainesville, Florida
HETA 88-199

October 1989

| | Urine Cadmium | | |
|---|---|---|---|
| Urine Analyte | 10 + ug/g creat | < 10 ug/g creat | p value[2] |
| Number | 32 | 59 | |
| NAGA (U/g creat) | 0.85 | 0.64 | 0.05 |
| AAP (U/g creat) | 6.14 | 4.97 | 0.02 |
| GGT (U/g creat) | 23.0 | 21.6 | 0.48 |
| RBP (mg/g creat) | 0.094 | 0.068 | 0.07 |
| Phosphorous (mg/g creat) | 57.3 | 63.0 | 0.24 |
| Calcium (mg/g creat) | 15.4 | 14.3 | 0.96 |
| Glucose (mg/g creat) | 8.6 | 8.7 | 0.93 |
| Total Protein (mg/g creat) | 44.5 | 49.7 | 0.23 |
| Albumin (mg/g creat) | 2.37 | 2.06 | 0.56 |
| Serum Analyte | | | |
| Creatinine (mg/dL) | 0.79 | 0.82 | 0.28 |
| Urea Nitrogen (mg/dL) | 13.0 | 13.7 | 0.37 |

1 - Adjusted for age, race, smoking, hypertension, diabetes, and nickel exposure.

2 - t-test (A p value less than or equal to 0.05 is considered to represent a "statistically significant" difference between the exposed and unexposed groups.)

# Cumulative Cadmium Exposure vs. Current Urine Cadmium Level

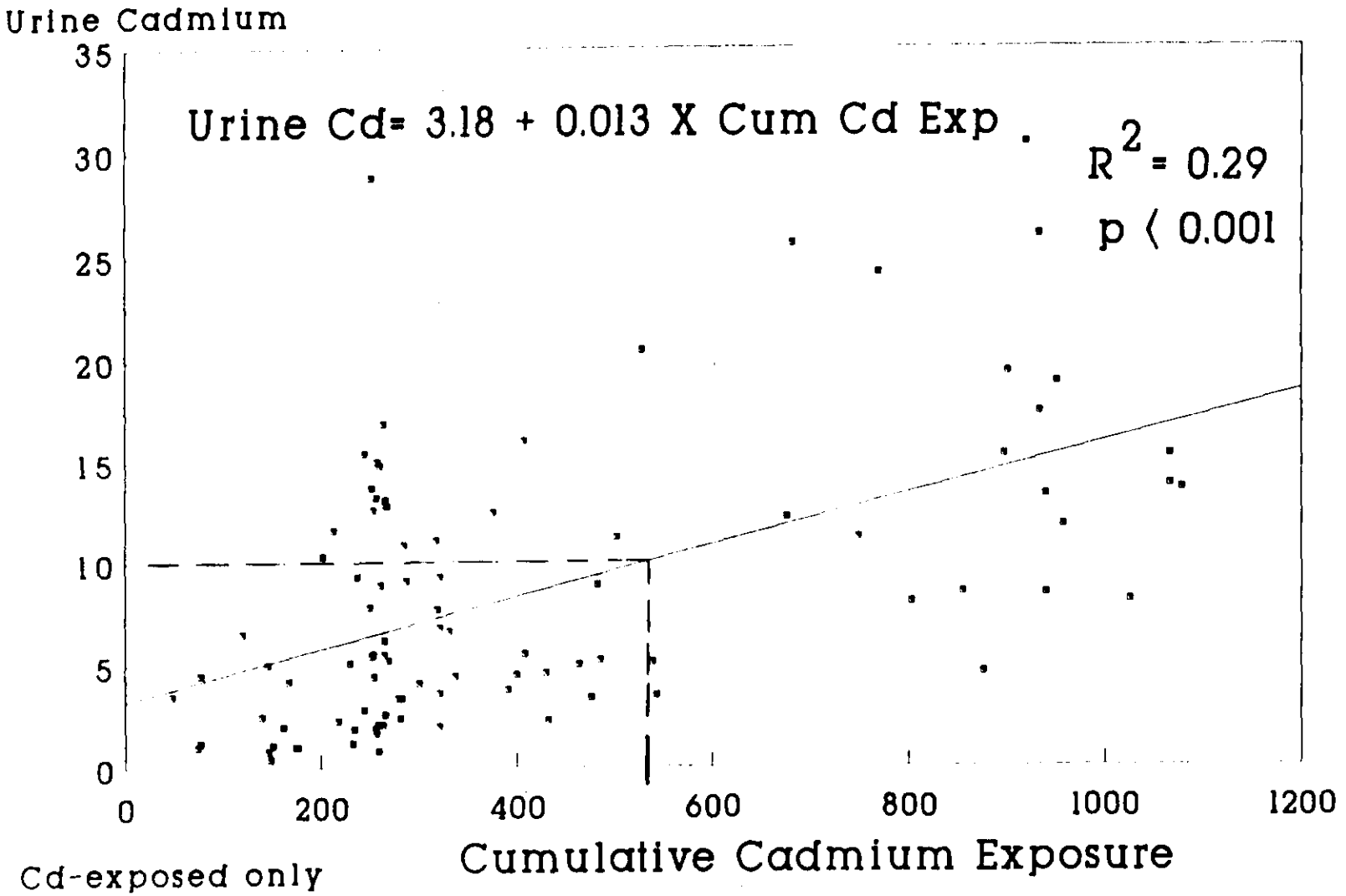


FIGURE 1

APPENDIX A

Laboratory Reference Values

| Analyte | Reference Range | Reference Source |
|---|---|---|
| Serum albumin | 3.4 - 5.0 g/dL | DuPont ACA Manual |
| Serum creatinine | 0.8 - l.3 mg/dL (Males) | " |
| | 0.6 - 1.0 mg/dL (Females) | " |
| Serum IgA | 57 - 414 mg/dL | " |
| Serum IgG | 508 - 1483 mg/dL | " |
| Serum IgM | 20 - 274 mg/dL | " |
| Serum phosphorous | 2.5 - 4.9 mg/dL | " |
| Serum retinol binding protein (SRBP) | 3 - 6 mg/dL | Literature[41] |
| Serum urea nitrogen (BUN) | 7.0 - 22.0 mg/dL | DuPont ACA Manual |
| CD3 (Total T Cells) | 60 - 80% positive | FACS manufacturer |
| CD04 (Total Helper Cells) | 34 - 54% positive | " |
| CD20 (Total B Cells) | 0 - 20% positive | " |
| NKH1 (%Natural Killer Cells) | 4 - 10% positive | " |
| Urinary albumin | 0 - 33.1 mg/L | CDC employees |
| Urinary alanine aminopeptidase (AAP) | 1.80 - 8.91 Units/L | " |
| Urinary beta-2 microglobulin (B2M) | < 300 ug/1 | LAB |
| Urine cadmium | 0.1 - 1.6 ug/L | NHANES III Pilot Study |
| Urinary gamma glutamyltransferase (GGT) | 5.19 - 83.51 Units/L | CDC employees |
| Urine glucose | < 30 mg/dL | DuPont ACA Manual |
| Urinary N-acetyl glucosaminidase (NAGA) | 0.17 - 3.50 Units/L | CDC employees |
| Urine nickel | 0- 5 ug/L | Literature[42] |
| Urine retinol binding protein (RBP) | 0.03 - 0.19 ug/mL | CDC employees |
| | 0.0 - 0.406 ug/mL | NHANES III Pilot Study |
| Urine total protein | ≤ l35 mg/L | DuPont ACA Manual |