HAZARD EVALUATION AND TECHNICAL ASSISTANCE REPORT
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MARTIN MARIETTA ENERGY SYSTEMS, INC.
HEALTH EVALUATION OF Y-12 WORKERS
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FORWARD

Revisions of each chapter were discussed between the principal investigator and the chapter's author. The principal investigator accepts responsibility for the entire final report. Our conclusions do not substantially differ from those of the preliminary report. While we have carefully considered critiques by outside reviewers, the responsibility of the final conclusions must rest with the University of Michigan research team.

Finally we would like to acknowledge the assistance provided by the management and the unions of Y-12. The support provided by several individuals enabled this study to be successfully completed: Kelly Cormier, Trudy Borset, Robert Kyle, William Akers, Edward Bailey, Dr. Shirley Fry, Dr. Donna Cragle, Philip Wallace, Julia McClanahan and Dolores Payne.

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INTRODUCTION AND BACKGROUND

Occupational exposure to elemental mercury has been associated with impairment or disease of several organ systems. The abnormalities most often associated with elemental mercury exposure have involved the renal system, and the peripheral and central nervous systems. Additionally, more recent studies have tentatively suggested that there may be adverse effects on the reproductive system. This investigation was undertaken to answer the following question: Is there an exposure-related relationship between occupational elemental mercury exposure at Y-12 and persistent health effects on the renal, reproductive, peripheral or central nervous systems? Measures were chosen that have been demonstrated to be sensitive to the effects of elemental mercury exposure in workers occupationally exposed. These include: (1) the one hole test and other tests in a neurobehavioral test battery adopted from Harvard (Baker, 1985) to measure motor function; (2) other tests adopted from the Harvard battery that measure sensory perception and nonverbal cognitive abilities; (3) clinical neurologic examination by a neurologist, including, quantitative measures of muscle strength, two-point discrimination, vibratory sensation, and pin-pain sensation; (4) forearm sustention tremor; (5) an electrodiagnostic evaluation of sensory and motor nerve conduction; (6) two measures of glomerular dysfunction: N-acetyl-b-glucosaminidase activity and albuminuria; and (7) level of fertility and adverse reproductive outcomes among workers and their spouses.

1. MATERIALS AND METHODS

Selection of Study Subjects

Elemental mercury was used at the Y-12 plant in the lithium program from 1953 to 1963. After lithium production was stopped, one of the two production facilities was dismantled during 1965-1966. Thus greatest elemental mercury exposure took place from 1953 to 1966 with a much lower level of exposure subsequently.

A cohort of workers occupationally exposed to elemental mercury was defined to include those workers who worked at least four months at the Y-12 plant between January 1, 1953 and December 31, 1966 (table 1-1). This time period was selected because it includes both the production and the later cleanup years. An earlier study (Cragle, 1984) on the mortality of workers exposed to elemental mercury used a similar cohort definition but restricted the years of employment to 1953-1958. In both studies, the group of workers was restricted to include only white males.

TABLE 1-1: Response Rate of Subjects

Group	Exposed	Non-exposed
Eligible for Study	2,136	6,801
Sample Selected	318	351
Not-contacted	28	25
Contacted	290	326
Contact Rate* (%)	(91.2)	(92.9)
Declined/Cancelled	41	71
Examined	247	255
Response Rate** (%)	(85.2)	(78.2)

*Contact Rate = (Contacted/Sample) x 100
**Response Rate = (Examined/Contacted) x 100

The mercury-exposed cohort was rank ordered based on cumulative lifetime (1953-1986) exposure to elemental mercury at the Y-12 plant; the exposure measure used was determined from the sum of the average quarterly urinary mercury measurements taken at the plant. This index (expressed in ug/L of urine) had a range of values from 2144 to 8572 (table 1-2). The study group was selected in descending order with the most heavily exposed workers selected first. Examinees and examiners were unaware of the rank ordering. Evaluations were conducted on 6 occasions between June 1985 and September 1986. An average exposure index by month studied for all exposed subjects follows:

TABLE 1-2:Cumulative Exposure By Study Month

Month	Number	Average (ug/L)
June 85	32	5706.1
October 85	49	4232.9
December 85	46	3407.2
March 86	53	3126.8
June 86	62	2612.6
September 86	5	2690.2
Average (s.d.)	247	3594.7 (1190.5)

The non-exposed group was selected from Y-12 plant workers employed during this same time period who supposedly were never exposed to elemental mercury and therefore never monitored for elemental mercury exposure. This selection used a frequency match to the mercury-exposed group within 5-year birth intervals, current job status (active or retired), and a 6-level job title categorization scheme based on final job title (table 1-4). The purpose of this matching was to control for age, educational attainment,

and job-related activity.

It was likely that some workers may have had job classifications where elemental mercury was used but who were not monitored for such exposure on the urinalysis program in 1953-1954 during program implementation. Similarly, an earlier study (Cragle, 1984), examined job title department combinations and the employment histories of the known mercury-exposed workers in 1953 and 1954. All workers in such job title-department combinations were included in the mercury exposure group even though urinalyses were not conducted. All workers assigned to these job and department combinations were identified and assigned a code for early non-monitored exposure. In all, 485 such workers were identified by this process. Two hundred and seventy of these 485 workers did not have a urinalysis during the period of January 1953 through December 1966 and hence were eligible for selection into the present study as non-exposed, but the matching process used did not select any of these subjects for inclusion in this study. Two hundred and fifteen workers on the urinalysis program during 1/1/53-12/31/66 were identified as possibly having mercury exposure in 1953 and 1954 as well. These workers were eligible for inclusion in the present study as mercury-exposed. The cumulative exposure measure used to select exposed workers identified 34 such individuals for inclusion in this study. By this measure the present study does not include any incorrectly classified non-exposed workers as exposed, but does include workers assigned an exposure index that probably is too low to 34 of the mercury-exposed workers. In addition to these two study groups, 82 volunteers were surveyed but they will not be included in the analysis because they were self-selected.

Characteristics of Subjects

table 1-3 presents the demographic characteristics of the individuals examined, divided into three groups: (1) Mercury exposed (Exposed), (2) Non-exposed (Controls), and (3) Self-selected volunteers (Volunteers). For volunteers no employment status was obtained.

TABLE 1-3:Demographic Characteristics

Characteristic	Exposed	Non-exposed	Volunteer
Number	247	255	82
Inactive [1]	174	182	NA
Active	73	73	NA
Mean Age (SD)	64.1(7.2)	64.2(7.3)	61.1(8.6)
Mean Education years (SD)	11.7(2.4)	11.8(2.6)	12.6(3.0)

1: No longer employed at Y-12.

The results of the job-title matching are presented in table 1-4. A complete breakdown of the job-titles in each of these six categories is given in appendix A.

TABLE 1-4:Job Title Classification

Job Category	Exposed N=247 Percent	Non-exposed N=255 Percent
Unskilled	2.3	0.5
Semi-skilled	36.5	31.9
Skilled	46.8	46.9
Supervisory	6.8	11.7
Clerical	0.9	1.4
Engineers	6.8	7.5

Test Procedures

Each subject was required to complete the following: a series of behavioral tests; a neurological examination; a quantitative measure of forearm tremor; a urinalysis; and a questionnaire covering work and medical history (appendix B). A subset of the entire cohort also underwent electrodiagnostic examination. Individual testing required a 3-4 hour single visit to the plant. Testing was conducted at the worksite in groups of four (2 exposed and 2 non-exposed) per hour over a sixteen month period. An equal number of exposed and non-exposed workers were scheduled per hour to minimize any time of day effects.

Medical/Lifestyle questionnaire. A trained research assistant interviewed each subject. Specific questions were asked about (1) medical history including diabetes, hypertension, and use of medications; (2) lifestyle habits including smoking, caffeine consumption, and alcohol consumption; and (3) exposures to known neurotoxins at Y-12, before Y-12, and from non-occupational sources (appendix B).

Behavioral evaluation.

The series of behavioral tests that were conducted measure two basic parameters in each of the subjects:(1) motor skills and (2) cognitive skills.

Motor skills:

One hole test. The One Hole test (Salvendy, 1975) measured fine motor dexterity by requiring subjects to repeatedly grasp, move, and position a very small pin in a close clearance hole. The number of times the pin was placed in the hole during a one minute period and the average time for each

step of the process was recorded by a microcomputer. Subjects repeated the task for five one-minute blocks. The primary performance score was the number of pins that the subject could insert per minute averaged across the last four one-minute blocks of testing.

Simple reaction time. This was a motor test of simple reaction time. The subject was required to press a button as quickly as possible following a visual cue from the video display terminal. The task was repeated 30 times using the index finger of each hand. Each subject's score was the average reaction time for the last 29 trials of the right and left hands. The test was selected from the Harvard battery as adapted by Baker (Baker, 1985).

Hand-eye coordination test. This test supplemented the tremor test, one-hole dexterity test, and psychomotor evaluations in the neurological examination. The subject used a microcomputer joystick to trace over a large sine wave pattern on the video display terminal. The computer moved a cursor horizontally at a constant rate, while the individual controlled the vertical motion of the cursor with the joystick. Deviations from a set line (as root mean square and mean absolute error) were recorded and constitute measures of coordination ability. Each subject performed the task four times and a root mean error score was based on the average of the last three trials. The test was selected from the Harvard battery (Baker, 1985).

Cognitive tests:

Short term memory span test. This test measured short term recall for a series of numbers of differing lengths. A list of numbers was presented on a microcomputer one digit at a time for one second each. Subjects were then asked to enter the digits using the computer keyboard in exactly the

same order as they were presented. This test was performed in two parts, the first determined an estimate of the subject's digit span and the second used this information to start a precision digit span procedure. The precision procedure used 40 trials - eight each at five different lengths of numbers. The test used the method of Smith and Langolf (Smith, 1983) to estimate the subject's digit span. This test required 20 minutes to perform.

Verbal ability. Each subject was asked to select the word, from a list of four provided, that had the meaning closest to the highlighted word shown on the video display terminal. In all, 25 words were shown. Each subject's score was calculated as the percentage correct. The test was selected from the Harvard battery (Baker, 1983).

Symbol-digit substitution. This was a test of visual/spatial ability. The Harvard microcomputer adaptation displayed nine symbols and digits at the top of the screen and the subject had to press the digit keys corresponding to a reordered test set of nine symbols. The time required to complete each symbol and the number of digits incorrectly matched were recorded. Five sets of nine symbol-digit pairs were presented, each subject's score was based on the average of the last four trials.

Benton visual retention test. This test has been administered in many standard neuropsychological batteries (Hanninen, 1982). The Harvard adaptation of this test was implemented on the IBM-PC microcomputer (Baker, 1983). The machine presented a test figure followed by four similar figures from which the subject selected the figure previously seen. The score consisted of the percentage of trials correct out of a total of 12.

Mood scale. An index of mood was measured on a 1-20 scale by having subjects rate themselves with respect to their feelings on 20 questions concerning 5 parameters over the previous seven days. The adaptation of this test (Baker, 1983) yields a five-dimensional mood profile (tension, depression, anger, fatigue, and confusion).

Clinical evaluation. One of two neurologists performed screening neurologic examinations on all subjects. An earlier test-retest evaluation showed that the two neurologists did not differ significantly in their grading on the same subjects. The screening examination included a subjective classification of proximal and distal strength, (normal, trace, mild, moderate, or severe) , upper extremity sustention tremor, coordination (fingers-to-nose, heel-to-knee), and muscle stretch reflexes (biceps,brachii, brachioradialis, quadriceps, and achilles). The presence or absence of pathologic reflexes was recorded (snout, jaw, Babinski responses) and distal lower extremity pulses were evaluated. Several quantitative tests of neurologic function were recorded including grip strength, touch-pressure sensation, two-point discrimination, and vibratory and pin-pain sensation.

Grip strength (Kg) for the dominant hand was determined using a Jamar hand dynamometer. Subjects squeezed the handle as hard as they could for 5 seconds. The maximum force for three 5-second trials was recorded.

Touch-pressure sensation was recorded using a pressure anesthesiometer (Research Media, Inc.). Stimuli were delivered to the dorsum of the dominant index finger and great toe. Subjects identified in which of two 3-second time intervals the stimulus was delivered. The task was repeated three times for each of progressively smaller stimuli until the subject

incorrectly reported the presence of the stimuli. The next largest stimulus was then taken as the threshold value if a subject correctly recognized all three trials.

Sweet's two-point compass calibrated in millimeters measured two-point discrimination for the dorsum of the dominant index finger and dorsolateral aspect of the ipsilateral foot. Beginning with the index finger, each subject was given a recognizable stimulus of 10 mm. Separation was decreased by 1 mm per trial until three consecutive responses of 1 point were obtained at the same distance. This was considered the threshold value if the subject correctly recognized the next increment of 0.5 mm. This was repeated on the foot beginning with a 30 mm separation, decreasing by approximately 2.5 mm per trial as described above. Once the descending threshold was defined, the subject had to correctly recognize the next increment of 2.5 mm. Failure to do so resulted in identifying an ascending threshold and repeating the trial as described above until the descending threshold was determined.

Vibratory sensation was determined for the dominant index finger and great toe using a 128-Hz tuning fork. Subjects reported when vibration could no longer be felt and the intensity of vibration was recorded using an acoustic vibrometer placed under the index finger or great toe. The descending threshold was recorded as the average of the last two of four trials. In the pilot evaluation, this technique was compared to a forced-choice technique in which the descending threshold was determined using a Sensortek vibrometer II. No significant differences were identified between the two techniques.

Pin-pain sensation was graded subjectively as in the conventional

clinical examination. Subjects were then asked to determine whether single stimuli at the index finger were equal to, less than, or greater than stimuli of approximately equal intensity at the upper forearms and they were asked to subjectively estimate the percentage of the smaller responses if they were different. This was repeated for the dorsum of the great toe and the upper calf. Responses were recorded as the ratio of the distal to proximal intensity.

Identified abnormalities on the screening neurologic examination resulted in additional clinical examination at the discretion of the neurologist (medication history, mental status evaluation, cranial nerve examination including opthalomoscopy, musculoskeletal examination, general medical examination). The additional evaluation was intended to identify specific medical or neurologic disorders that could complicate data analyses (familial tremor, peripheral vascular disease, entrapment mononeuropathy, traumatic radiculopathy or myelopathy, etc.).

The results of the clinical examination were summarized as normal or abnormal. Abnormal examinations were further identified as having evidence of a polyneuropathy (equivocal or unequivocal), tremor, or other diagnoses. The latter were not individually coded but were listed specifically and then used to form subgroups upon which further analyses were stratified (see statistical methods).

Quantitative Tremor Measurement. The basic tremor apparatus was the same as the forearm pointing device used by Langolf et al. (Langolf, 1978; Langolf, 1981). This device measured sustention tremor of the forearm about the elbow joint. The subject's elbow was placed on a rest, and his hand supported the pointer arm by grasping a pistol grip. A linear

potentiometer provided a hinge at the elbow end of the pointer and converted tremor of the forearm to an electrical signal that was amplified and input to an IBM personal computer for spectral analysis. The signal was displayed on a meter. The subject was instructed to hold the meter's needle as steady as possible to a center mark on the meter scale. The displacement signal from the potentiometer was sampled by the computer at a frequency of 50 Hz for 2.6 minutes. The resulting computed power spectrum had a width of 25 Hz, broken into separate 0.2 Hz width power bands. Computed performance parameters included root mean square (RMS) tremor amplitude, average absolute tremor amplitude, mean spectrum frequency and percentage of total power in the single 0.2 Hz band that had the highest power in the 4 to 8 Hz neuromuscular tremor frequency range. The latter parameter, called neuromuscular peak power, was the parameter of primary interest in previous work with mercury exposed subjects (Langolf, 1978; Langolf, 1981). For this study, a new displacement tremor parameter was added, the percentage of total spectrum power in the 4-8 Hz range. This summated measure of neuromuscular tremor should be more statistically reliable than the neuromuscular peak power that is quite variable because it depends on estimated power in only one 0.2 Hz band.

New to this study, an accelerometer was attached to the pointing apparatus' pistol grip handle. The accelerometer's signal was amplified and subjected to spectral analysis using the same methods as displacement tremor. Since acceleration power is proportional to the fourth power of frequency, the resulting tremor spectrum emphasizes higher frequencies compared to displacement tremor which has a mean power frequency of about 1.2 Hz due to ballistic impulses from the heart beat. Acceleration tremor

may therefore provide a purer, more reliable measure of neuromuscular tremor which occurs at frequencies above 4 Hz. Acceleration tremor parameters which were computed included RMS amplitude, average absolute amplitude, total power in the 4 to 8 Hertz band, and mean power frequency.

Electrodiagnostic evaluation. Nerve conduction studies were performed on the right ulnar (motor and sensory), median (sensory), sural (sensory), and tibial (motor) nerves, using conventional techniques. Hand and foot surface temperatures were measured for all subjects, and the extremities were warmed if they were less than 31 C. Negative peak amplitude, distal latency, and maximum conduction velocity were measured for each subject.

Urinary tests. The heavy weight protein selected for evaluation was N-acetyl-B-glucosaminidase (Price, 1970). Urinary samples consisted of a spot sample taken anytime during the three hour period the subject's were being tested. Split samples were used for validation, some samples were split and reanalyzed in the same lab while some samples were sent out to a second lab for independent testing. Correlation on albumin, creatinine, protein, and N-acetyl-B-glucosaminidase was very good, .96, .99, .99, .99 respectively, while the correlation on mercury levels was lower due to the large number of subjects with levels near the lower limit of detection of the test procedure being used (<4.0 ug/L).

The urine samples collected in this study for analysis were single spot samples taken between 8:00 am and 4:00 pm. In addition to BNAG, total protein, albumin, creatinine, and mercury were measured. Since none of the measurements in this study involved timed urine samples, adjustments were made for different volume levels by expressing all concentrations per gram of creatinine excreted in the urine (Elkins, 1974).

All samples were immediately frozen after collection. Samples remained frozen for transport to the University of Michigan, where they were thawed at room temperature for analysis. Albumin in urine was quantified using a modification of the serum albumin turbidimetric immunoassay protocol suggested by Atlantic Antibodies for use on the Roche Cobas-Bio centrifugal analyzer (Sathianathan, 1986). Urine protein was quantified by an adaptation of the Bradford Coomassie dye binding procedure on the Cobas-Bio (Bradford, 1976; Giacheriv, 1984). Dye reagent and calibrate were obtained from Quantimetrix Corp., Hawthorne, CA, 90250 . Urine creatinine was measured by the standard Jaffe reaction as adapted to the Technicon RA-1000 (Knoll, 1986). N-acetyl-B-glucosaminidase was analyzed by Powell's modification of a fluorimetric assay technique developed in 1961 (Powell, 1983; Leabeck, 1961). Urinary levels of mercury were made by flameless atomic absorption (Henderson, 1978).

Reproductive questionnaire. The analysis of reproductive health is limited to ever married subjects in the mercury-exposed and the mercury non-exposed (control) group. Five subjects in the mercury-exposed group and one subject in the non-exposed group were excluded because they never married and never fathered children. There was one refusal in the exposed group. In cases of multiple marriages, only the marriage closest to the time period under study (1953-1966) was included. Thus, the analysis was restricted to the data collected on 241 mercury-exposed and 254 mercury non-exposed subjects, a total of 495 subjects.

A structured interview with each subject was used to obtain information on the wife's demographic characteristics, the wife's occupational and general health history, and reproductive health history of

the couple (see appendix 2B). Each interview lasted between 30 and 60 minutes depending on the number of children.

To check the reliability of these data the same information was collected by telephone interview from a subset of the subjects' wives. A stratified random sample procedure was used to select this sample of wives (stratified on exposed vs. non-exposed and study month). 94 subjects were selected in this process (Table 1-5, next page). 31 subjects were excluded for several reasons: they had never married, they had not given permission for their wives to be contacted by phone, the wife was deceased, the ex-wife could not be located, or there was no answer over several weeks of calling. There was only one refusal.

Comparison (pair-wise t-test) of answers provided by subjects and their wives by exposure group (table 1-6) showed a statistically significant difference in the non-exposed group in number of children born with abnormalities ($t=2.41$, $p=.02$). In addition, there was lack of agreement on children's birthweight, especially first and second born (child #1: $t=2.86$, $p=.006$; child #2: $t=2.54$, $p=.01$) with husbands tending to remember higher birthweights than wives. Quite often, however, husbands stated that they did not recall birthweights. Similarly, there was lack of agreement on prematurity, especially of first born children ($t=3.24$, $p=.002$). For these reasons, prematurity and low birthweight were not analyzed as outcome measures in this analysis.

Table 1-5:

TELEPHONE INTERVIEWS WITH WIVES (June 1985-June 1986)

Month	Status HG	Status Cont	Number Selected	Number Refused	NA[1]	Other[2]	Total Completed	Completed By Status HG	Completed By Status Cont
June, 1985	10	9	19	1	0	3	15	8	7
October, 1985	10	10	20	0	7	0	13	7	6
December, 1985	10	10	20	0	5	2	13	6	7
March, 1986	10	11	21	0	5	2	14	5	9
June, 1986	7	7	14	0	4	2	8	3	5
Total	47	47	94	1	21	9	63	29	34

1 This includes: (1) Permission to call not granted (wife or ex-wife).
(2) Ex-wife unlocatable though permission was granted.
(3) Wife deceased.

2 This Includes: (1) Never married-Never fathered.
(2) No answer for 5-plus calls.

When breaking down abnormalities and illnesses by type, husbands and wives often did not agree on the specific nature of the problems. Lack of agreement on these outcome variables requires caution in any interpretation of the relationship between exposure and children born with abnormalities and illnesses in the larger study.

TABLE 1-6:
Comparison of Answers Obtained from Husbands and Wives by Exposure Group

Characteristic Compared	Exposed (N=29) Husbands Mean(s.d.)	Wives Mean(s.d.)	paired t-test sig	Non-exposed (N=34) Husbands Mean(s.d.)	Wives Mean(s.d.)	paired t-test sig
Number of Liveborn Children	2.79(1.21)	2.83(1.17)	.33	2.47(1.62)	2.56(1.46)	.37
Number of Still-births and Miscarriages	0.59(1.05)	0.62(1.01)	.75	0.35(0.95)	0.44(1.13)	.26
Number of Pregnancies	3.38(1.66)	3.45(1.74)	.45	2.82(1.82)	3.00(1.76)	.16
Number of Liveborn with Abnormalities [1]	0.17(0.47)	0.10(0.31)	.42	0.21(0.48)	0.0	.02
Number of Liveborn with Illnesses [2]	0.31(0.66)	0.31(0.54)	1.00	0.41(0.86)	0.21(0.48)	.16

1. Abnormalities include: Down's Syndrome, cleft palate, club foot, heart defect, kidney defect, "other".
2. Illnesses (in childhood) include: cancer, kidney problems, nervous problems, mental retardation, small for age, surgery as child, failed grade/ special education,"other".

Statistical Methods

The overall analysis was divided into four main sections:

(1) Selection of response variables for further analysis.

(2) Preliminary evaluation of subjects.

(3) Group comparisons between exposed and Non-exposed workers.

(4) Dose-response relationships between functional measures and urine mercury exposure variables.

Selection of response variables. It was likely with the large number of outcomes examined in this study, that some would be found to be "significant" by chance alone. To minimize this problem, a subset of important response variables were identified for evaluation before the final analysis took place. The most important response measures and the most important characteristics to adjust for were determined before the actual analysis was conducted.

Covariates were determined in one of two ways: 1) covariates known to be important were selected before the analyses were conducted; 2) using stepwise regression techniques covariates of potential interest were selected if they had a significant effect on the outcome being analyzed. Due to the known effect of aging on the nervous system as well as on the other outcomes under investigation, it was determined ahead of time that age would be used as a covariate when analyzing all outcome measures.

The response variables of greatest interest were divided into the following categories:

(a) Medical history

(b) Behavioral (psychological) performance

(c) Clinical neurological examination

(d) Quantitative tremor measurements

(e) Electrodiagnostic evaluation

(f) Renal measurements

(g) Reproductive history

Preliminary evaluation of subjects. To study the effects of mercury upon the neurologic system, subjects were examined to identify known or suspected medical conditions or clinical abnormalities unrelated to mercury exposure that could result in neurologic impairment. Historical and clinical information was collected during the neurologic examination, after which each subject's performance was classified as normal or abnormal. If abnormal, the neurologist identified an etiology, if known, that would explain the neurologic findings. In all, 52 clinical disorders were identified that could account for abnormal performance in 129 subjects. These subjects were designated the exclusion group and the remaining subjects were designated the restricted group.

This information was used in two ways in evaluating potential neurologic abnormalities associated with mercury exposure: 1) subjects identified as having known or suspected conditions unrelated to mercury exposure were excluded from subsequent analyses; and 2) all subjects were included in the analyses but dummy variables were added to adjust for each subject's non mercury related clinical status.

To define further the exclusion group of subjects, the 52 clinical conditions identified during the examination were classified into 10 groups of presumed known etiology, with the remaining more poorly defined conditions grouped together as 'unknown etiology'. Of the 42 conditions of known etiology, 4 were later classified as normal because they were not associated with any apparent clinical abnormality or were deemed unassociated with neurologic disease. Table A summarizes the categorization of the identified abnormalities.

Table A

Grouping of Conditions Identified from the Neurologic Evaluation that Could Result in Neurologic Impairment Unrelated to Mercury Exposure

Connective tissue disorder: active rheumatoid arthritis, severe gout.

Inflammatory: history of severe meningitis, prior poliomyelitis

Metabolic: diabetes mellitus (insulin dependent and non-insulin dependent).

Neoplasm with or without chemotherapy or radiation therapy: chronic lymphocytic lymphoma, hepatoma, lymphoma, pancreatic carcinoma, spinal cord tumor.

Nutritional: documented Vitamin B12 deficiency with prior gastrectomy.

Psychiatric: current Stelazine use, prior electroconvulsant therapy, severe depression.

Structural: carpal tunnel syndrome, cervical radiculopathy, cervical spondylosis, lumbosacral radiculopathy, spinal stenosis.

Toxic or medication exposure: alcohol use, Dapsone, Theophylline, Valium.

Trauma: foot injury, hand injury, prior frostbite, traumatic encephalopathy.

Vascular: cerebral hemorrhage, cerebral infarction, severe peripheral vascular disease.

Suspected: abnormal tremor plus evidence of Parkinsonism, idiopathic postural hypotension, tremor with remote family history of similar tremor, undefined progressive dementia, myelopathy (undefined level).

Group comparisons between mercury-exposed and non-exposed workers. The primary objective of these analyses were to examine differences in response variables between the workers exposed to mercury and the workers not-exposed. Comparisons were made using the Mann-Whitney U statistic for continuous outcomes and Chi-Square statistic or Fisher Exact Test for categorical outcomes. Covariance analyses were used to adjust comparisons of the exposed and non-exposed groups for such covariates as age and lead exposure.

Dose-response relationships. The comparison between groups also included regression analysis. The purpose was to identify associations between urine mercury exposure measures and response on a given test. A measure of cumulative lifetime exposure and a measure of the single highest peak exposure were selected for regression analysis (Section 2. Exposure Assessment). These urine history exposure variables were used in multiple linear regression models. The partial correlation coefficient for the urine mercury exposure variable indicates the relative contribution of this exposure on the response when other factors in the model have been accounted for.

2. EXPOSURE ASSESSMENT

Other studies have used a variety of exposure measures to quantify individual dose. In those studies that have used urinary mercury levels, many (Camerino, 1982; Lauwerys, 1977; Piikivi, 1984) have been based on a time weighted average (TWA); others (Baker, 1985; Hanninen, 1982; Langolf, 1981; Mattiussi, 1982) have been based on the number of readings or quarters with a reading above an arbitrarily selected level (usually 0.3 or 0.5 mg/L). Still other studies (Fawer, 1983; Miller, 1975) have been based on duration of exposure to mercury in quarters or years.

The urinalysis program at Y-12 was instituted in 1953 in conjunction with mercury use in the lithium program. A Plant Action Value (PAV) was set at 0.3 mg/L of urine. Workers exceeding this level were brought to the attention of their supervisor. Workers who had urinary mercury levels above 0.6 mg/L were removed from exposure areas.

Mercury Variables

Although selection of the exposed group was based on cumulative lifetime urine mercury (see selection of subjects) at the Y-12 plant, this may not be the best exposure measure to predict impairment (Langolf, 1981). Therefore, mercury exposure was characterized in a number of different ways. All mercury exposure measures considered were based on the Y-12 urinalysis records. The names and a brief description of each follows:

HGU-LEQU: Urinary mercury lifetime equivalent quarter units. A measure of integrated exposure to mercury at Y-12 calculated by taking the sum of the average urinary level for every quarter in which such readings were taken. The level of this variable was the basis for selection into the exposed group.

HGDUR: Duration of mercury exposure. This variable is a count of the number of quarters each individual had urinary mercury readings taken which had a detectable amount of mercury present in the urine.

HGPAV: Individual readings above the Plant Action Value (PAV) of 0.3 mg/L. A count of the number of quarters each individual had urinary mercury test readings greater than or equal to 0.3 mgHg/liter of urine.

HGPAV2: Individual readings above 0.6 mg/L. A count of the number of quarters each individual had urinary mercury test readings greater than or equal to 0.6 mg/liter of urine.

HGPEAK: Single highest urinary mercury reading. This variable gives the level of each individual's single highest urinary mercury reading recorded between January 1, 1953 and December 31, 1966.

HGAVE: The average urinary value for each individual between January 1, 1955 and December 31, 1956. If more than one reading was taken in a given quarter the average of all readings for the quarter were used in this calculation.

HGUAVE: Total lifetime exposure (ug/L) divided by number of quarters exposed. An average of the lifetime exposure at Y-12 for the time exposed between 1953 and 1966.

Figure 2-1 presents a correlation matrix for all of these measures of mercury exposure. Note that the HGU-LEQU value based on cumulative exposure is positively correlated with all of the other measures, and that HGDUR the duration measure is negatively correlated with all the other measures. The fact that the duration measure is negatively associated with all the other exposure variables indicates that most of the exposure occurred at high levels over a short period of time. The three measures based on specific high exposure levels, HGPAV, HGPAV2, and HGPEAK, are all highly correlated with each other as well as with HGAVE and HGUAVE. The high correlation between HGUAVE and HGAVE (r=.845) suggests that most of the total recorded mercury exposure took place during the short period of time, 1955-1956, for which the HGAVE variable was calculated.

FIGURE 2-1: Correlation Matrix of Mercury Exposure Variables

Correlation Matrix CASES=HGSTATUS:HG

N= 242 DF= 240 R@ .0500= .1261 R@ .0100= .1653

VARIABLE							
HGU-LEQU	1.0000						
HGDUR	.4312	1.0000					
HGPAV	.6906	-.1464	1.0000				
HGPAV2	.3220	-.3331	.4940	1.0000			
HGPEAK	.3855	-.2570	.4600	.7144	1.0000		
HGAVE	.3446	-.5072	.5814	.7014	.6291	1.0000	
HGUAVE	.1732	-.6874	.5447	.6587	.5264	.8451	1.0000
	HGU-LEQU	HGDUR	HGPAV	HGPAV2	HGPEAK	HGAVE	HGUAVE

Many analyses were limited to HGU-LEQU, HGPAV2, and HGPEAK. The correlations between these three exposure indices are highlighted in the figure. The cumulative exposure measure (HGU-LEQU) was chosen for its integration of both level and length of exposure, the HGPAV measure was selected because it was concerned with repetitive exposure above a level considered to have an adverse effect in past studies, and the HGPEAK measure was selected because it measures the single highest short term mercury level of each individual.

A limitation of the exposure variables is that the actual urinary measurements made at Y-12 may not accurately reflect each worker's exposure since urinary measurements were usually made only once every ninety days and sampling intervals often exceeded 90 days. As a result, brief exposures such as those following a mercury spill, might have been missed. This kind of problem would have two effects: (1) the exposure level of an exposed worker may have been underestimated; (2) an exposure that occurred to a non-exposed worker may have gone completely undetected. This type of misclassification would tend to reduce the apparent effect of mercury exposure in comparisons of the exposed with the non-exposed.

Ninety-four (36.9%) of the workers selected as non-exposed reported exposure to mercury on a checklist of possible chemical exposures included in the health questionnaire. A plan to review the Y-12 employment records of these workers is underway, to determine if they contain job titles, calendar year, and department combinations where mercury may have been used. This process will serve as validation for the urinalysis results obtained at Y-12.

3. GENERAL CHARACTERISTICS

The exposed and the non-exposed groups were generally similar on any potential study confounders and health conditions reported on the Health Questionnaire. Reported use of alcohol was slightly higher in the non-exposed group, while both groups reported a level higher than their current level for consumption of alcohol in their past.

TABLE 3-1: General Characteristics of the Study Group

Characteristic	Exposed Mean(s.d.)	Non-exposed Mean(s.d.)	Signif.
Cigarette smoking:			
Current smokers (%)	24.7	21.2	.17
Alcohol consumption:			
Current alcohol use (%)	25.9	32.9	.08
No. of drinks/wk	5.7 (4.5)	6.8 (5.2)	.15
Past alcohol use (%)	33.6	33.7	.33
No. of drinks/wk	8.6 (5.3)	8.2 (4.3)	.69

Signif. for % = Chi-Square with 1 d.f.
Signif. for No. drinks = student t-test (two-sided)

The exposed group reported having cancer of any kind at a rate nearly twice that of the non-exposed group (11.7% vs. 6.7%). This difference was statistically significant (chi square=3.9; p=.05), even though a previous study on this same group of workers (Cragle, 1984) did not show significant differences in deaths due to cancer among these workers determined from reported causes of death. A distribution of these reported cancers is given by exposure status in table 3-2. As expected, skin cancer is the type most frequently reported. Three workers in the mercury-exposed group reported cancer, but did not specify the site. The proportion of subjects reporting hypertension and diabetes was similar for the two groups (table 3-3). The proportion of individuals currently seeing a doctor or currently

taking medication was also similar. The number of individuals reporting tremor was higher in the exposed group but was not statistically significant (p=.09).

TABLE 3-2: Distribution of Reported Cancer Cases *

Cancer Site	Exposed N=29 Number (%)	Non-exposed N=17 Number (%)
Ever Reporting:		
Skin	8 (27.6)	4 (23.5)
Prostate	5 (17.2)	3 (17.6)
Bladder	4 (13.8)	3 (17.6)
Lung	0	2 (11.8)
Stomach	0	1 (5.9)
Liver	1 (3.4)	1 (5.9)
Lymphoma (CLL)	2 (6.9)	0
Pancreas	1 (3.4)	0
Other [1]	5 (17.2)	3 (17.6)
Not Specified	3 (10.3)	0

* Includes seven interviews conducted by telephone.
1 Other: lip, vocal chord, clavicle, nasal, and melanoma.

TABLE 3-3: General Medical History and Mood of the Study Groups

Characteristic	Exposed	Non-exposed	Signif.
Ever Reporting:			
Cancer(%)	11.7	6.7	<.05
Hypertension(%)	36.9	42.0	.26
Diabetes(%)	12.4	10.3	.45
Tremor(%)	10.0	5.8	.09
History of family tremor(%)	6.3	6.2	.97
Heart disease(%)	20.6	25.9	.19
Currently:			
Seeing a doctor(%)	61.4	55.8	.23
On a medication(%)	60.6	56.8	.40
Psychomotor Evaluation:	Mean(s.d.)	Mean(s.d.)	Signif.
Tension (#/5)	2.5 (0.7)	2.4 (0.7)	.24
Depression (#/5)	1.8 (0.7)	1.8 (0.7)	.48
Anger (#/5)	1.7 (0.6)	1.7 (0.6)	.57
Fatigue (#/5)	2.9 (0.8)	2.8 (0.8)	.11
Confusion (#/5)	2.3 (0.6)	2.3 (0.6)	.66
Mood Score Total (#/25)	11.2 (2.6)	11.0 (2.5)	.39

Signif. for %: Chi-Square with 1 d.f./ For means: Student t-test (two-sided)

An evaluation of mood was conducted as part of the psychomotor test battery. Subjects were similar with respect to the five measures evaluated, tension, depression, anger, fatigue, and confusion. Each factor was scored on a scale of 1-5. The mean mood scores of both groups were not significantly different.

Characteristics of Subjects that Refused to Participate or Cancelled their Appointment for Examination.

There were 72 workers selected for the comparison group that refused to participate or cancelled their appointment and 39 such workers in the exposed group. A follow-up interview to ascertain a general description of this group was conducted by telephone. 80 interviews were completed in this process, 52 (72.2%) were completed in the comparison group and 28 (71.8%) were completed in the mercury exposed group. There was not a significant difference in these response rates.

TABLE 3-4: Follow-up of Subjects Not Examined

Contact Group	Comparison	Exposed
Refused or Cancelled	72	39
Telephone Interview w/ Refused or Cancelled	52 (72.2%)	28 (71.8%)

This group of workers interviewed by telephone was significantly older than the group of workers examined in this study (67.8 vs. 64.2; t-test, p=.03). The only other factor that was different between these two groups was current level of alcohol use. The group interviewed by telephone was

probably less likely to report sensitive information about alcohol use than those that underwent extensive examination, making this difference unmeaningful. Also interesting, was the finding that workers in the telephone group reported exposure to mercury at a rate higher than indicated by their Y-12 exposure records (77% vs. 35%), a similar finding has already been reported for the group of workers examined.

TABLE 3-5: Comparison of Subjects Examined with Subjects Not Examined By Mercury Exposure Group: Demographic and Lifestyle factors

Characteristic	EXPOSED TO MERCURY			NOT EXPOSED TO MERCURY		
	Exam (N=247) Mean (s.d.)	No-Exam (N=27) Mean (s.d.)	t-test / chi-square Sig.	Exam (N=255) Mean (s.d.)	No-Exam (N=53) Mean (s.d.)	t-test / chi-square Sig.
Age (years)	64.1 (7.2)	70.1 (9.1)	<0.001	64.2 (7.3)	66.6 (8.0)	.03
Education (years)	11.7 (2.4)	11.7 (1.5)	.50	11.8 (2.6)	11.2 (3.0)	.15
Cigarette Use:						
Current use	24.7%	29.6%	.55	21.2%	26.4%	.30
Alcohol Use:						
Current Use	25.9%	11.1%	.08	32.9%	15.1%	.01
Ave. drinks/wk	5.7 (4.5)	2.0 (0.0)	.24	6.8 (5.2)	11.5 (11.0)	.06
Reported Exposure:						
Uranium	91.9%	88.9%	.90	82.7%	73.6%	.28
Lead	39.4%	59.3%	.01	49.4%	49.1%	.72
Mercury	98.4%	100.0%	.48	36.9%	66.0%	<0.001

The subjects Examined did not differ from those Not-examined in the rate of reported health conditions for those factors considered to be important to the outcomes investigated (tremor, hypertension, diabetes). Nor, did they differ on other health conditions or practices about which they were asked. There was a significantly higher reported rate of

exposure to mercury among the Not Exposed for those subjects not examined as compared to those that were examined.

TABLE 3-6: Comparison of subjects Examined with Subjects Not Examined By Mercury Exposure Group: Reported Health Conditions and Habits

Characteristic	EXPOSED TO MERCURY			NOT EXPOSED TO MERCURY		
	Exam (N=247) Mean	No-Exam (N=27) Mean	t-test / chi-square Sig.	Exam (N=255) Mean	No-Exam (N=53) Mean	t-test / chi-square Sig.
Ever Reporting:						
Cancer	11.7	14.8	.58	6.7	5.7	.77
Hypertension	36.9	48.1	.18	42.0	39.6	.72
Kidney Disease	11.8	7.4	.54	9.0	3.8	.20
Diabetes	12.4	22.2	.13	10.3	5.7	.31
Tremor	10.0	18.5	.17	5.8	9.4	.32
History of tremor	6.3	3.7	.65	6.2	9.4	.44
Heart disease	20.6	40.7	.02	25.9	28.3	.72

4. RESULTS: OVERVIEW

Unadjusted and Adjusted Group Comparisons

A number of different outcomes were examined for each subject. As an overview, this section presents the average performance by the exposed and the non-exposed groups on the outcomes selected for possible investigation. The Mann-Whitney U test, was used to compare the mean performance of these two groups because it does not assume a normal distribution. Covariance analysis also was used to compare the mean performance of these two groups by adjusting for the contribution due to other factors on the outcome under consideration. The other factors (covariates) included in the covariance test, depended on the particular outcome measure under investigation. A significance level of < 0.10 was used in these overall group comparisons for selection of which outcome measures may be of interest for more detailed examination.

While reported uranium exposure was significantly higher in the mercury exposed group, this variable was not found to be significantly associated with the outcomes under investigation when using stepwise regression. Reported lead exposure was significantly higher in the non-exposed group than in the exposed group and was found to be significantly associated with many of the outcomes under investigation in stepwise regression analyses.

TABLE 4-1: Occupational Exposure of the Study Groups

Characteristic	Exposed	Non-exposed	Signif.
Ever Exposed:			
Uranium % (reported)	91.9	82.7	.004
Lead % (reported)	39.4	49.4	.03
Current Level:			
Urine Mercury (ug/L)	5.7 (7.1)	6.5 (9.6)	.21 a.

Signif. = Chi-Square with 1 d.f.
a. Signif. = Mann Whitney U.

Current level of urinary mercury was higher in the non-exposed group than in the exposed group. The normal level for urinary mercury is up to 20 ug/L. The level of mercury in both groups was near the limit of detection (5ug/L) for the technique used and, as such, displayed high relative variability.

Behavioral tests

Of the seven tests in the behavioral battery, the reaction time test and the hand-eye test had p-values less then 0.10 for the Mann-Whitney test (table 4-2). The covariance test adjusted for both age and years of education. These covariates were selected due to their known importance on the outcome of these tests. After these adjustments, both the reaction time test and the hand-eye coordination test had a p-value less than 0.10. The difference for the hand-eye test was very significant (p=0.004).

TABLE 4-2
GROUP COMPARISON: Psychomotor Results

Response	Exposed N=247 Mean(s.d.)	Non-exposed N=255 Mean(s.d.)	Mann-Whitney Signif	Covariance a Signif
1. Motor tests				
A) Reaction Time (msec)	379.5 (58.2)	371.2 (55.4)	.08*	.07*
B) Number of Pins (One Hole)	27.3 (6.9)	28.0 (7.5)	.21	.35
C) Hand-eye (RMS)	8.1 (4.0)	7.2 (3.5)	.004***	.004***
2. Cognitive tests				
D) SymbolDigit (% cor)	97.1 (4.9)	96.8 (5.7)	.90	.48
Reaction time (sec)	3.71 (1.2)	3.64 (1.2)	.32	.58
E) VisualMemory (% cor)	70.4 (18.0)	70.0 (17.9)	.70	.82
Reaction time (sec)	8.29 (3.1)	8.31 (3.4)	.99	.91b
F) Vocabulary (% cor)	65.2 (18.6)	66.4 (18.8)	.53	.53
G) Digit Span	5.4 (1.0)	5.5 (1.0)	.23	.16

* p<.10, ** p<.05, *** p<.01
a. Adjusting for age (years), education (years) and lead exposure (no,yes).
b: Significant interaction, for differences in coefficients of adjustors.

Neurologic Examination

The motor examination variables were graded on a five point scale with none followed by four increasing levels of response. The variables were analyzed as none vs. any type of positive response. In the motor examination, proximal strength, distal strength, and sustention tremor, a p-value less than 0.10 was found for proximal strength (table 4-3).

TABLE 4-3
GROUP COMPARISON: Neurologic Examination

Response	Exposed N=247	Non-exposed N=255	Fisher Exact	Logistic
motor examination:	Percent Abnormal		Signif	Signif
strength:				
Proximal (%)	2.4	0.0	.02**	.24
Distal (%)	4.9	2.0	.1	.08*
Grip (Kg)	42.9	44.0	.21	.12
tremor:				
Coordination-arms (%)	19.1	13.8	.14	.12
Coordination-legs (%)	3.7	2.8	.76	.48
Sustention Tremor (%)	32.5	26.8	.20	.11
sensory examination:	Mean(s.d.)	Mean(s.d.)	Mann-Whitney Signif	Covariance Signif
Joint Pos. Sensation (#/10)				
HAND:	0.02(0.18)	0.02(0.13)	.71	.66
FOOT:	0.29 (1.1)	0.19 (0.8)	.26	.25b
Pin-pain sensation (proximal/distal)				
HAND:	187.8(110.8)	178.3(110.4)	.16	.30
FOOT:	130.1 (81.9)	122.7 (78.3)	.36	.35
2-pt. Discrimination (mm)				
HAND:	4.7 (2.0)	4.5 (1.5)	.51	.16
FOOT:	34.3 (17.5)	32.4 (11.9)	.32	.14b
Touch Sensation (gms)				
HAND:	3.6 (0.4)	3.5 (0.4)	.19	.09*
FOOT:	3.9 (0.5)	3.8 (0.4)	.41	.12b
Vibration (sec)				
HAND:	8.5 (2.6)	8.2 (3.2)	.14	.24
FOOT:	15.9 (5.1)	15.5 (4.9)	.59	.24
reflex examination:				
muscle stretch reflexes:				
Biceps	3.9 (1.0)	3.9 (1.0)	.86	.87
Brachioradialis	3.8 (1.0)	3.8 (1.0)	.97	.92
Quadriceps	4.3 (0.9)	4.3 (0.9)	.89	.81
Achilles	3.6 (1.1)	3.5 (1.3)	.24	.22
pathologic reflexes:	Percent Abnormal		Fisher Signif. b.	Logistic Signif c.
Babinski (%)	3.7	1.6	.24	.16
Jaw (%)	8.6	7.1	.66	.44
Snout (%)	42.3	34.3	.08*	.07*

* p<.10, ** p<.05, *** p<.01
a. Adjusting for age (years), education (years) and lead exposure (no,yes).
b. Signif. for % = Fisher Exact test of cell frequencies.
c. Adjusted Signif. for % = Logistic Regression

None of the quantitative measures from the neurologic examination displayed a significant difference between the mercury exposed and the non-exposed when using the Mann-Whitney test (table 4-3). One measure (touch sensation in the hand) had a p-value less than 0.10 in the covariance analysis after adjustment for both age and lead exposure.

The outcome measures in the reflex examination were graded on an ordinal scale and as such were analyzed as a continuous response. In both the Mann-Whitney and the covariance analysis none of these measures had a p-value less than 0.10.

The pathologic reflexes were scored as none vs. positive with positive indicating the presence of impairment on the outcome being evaluated. The mercury-exposed group had more pathologic reflexes on all three measures, but only the snout evaluation was statistically significant below the 0.10 level (table 4-3).

The clinical neurologic examination was summarized as either a normal examination or not a normal examination. In those cases where the examination was not normal, a further summary of the type of abnormality present was made. These included the presence of abnormal tremor or polyneuropathy. These were graded positive, equivocal, or absent. In the group comparison analysis, the equivocal findings were grouped with the normals and the percent positive for each abnormality were compared using the Fisher exact test. None of these summary measures was found to be statistically significantly different between the two groups (table 4-4).

TABLE 4-4
GROUP COMPARISON:Exam Summary

Response	Exposed N=246 Percent Abnormal	Non-exposed N=254	Fisher Exact Signif
Normal Exam	47.4	48.4	.88
Polyneuropathy	13.8	16.5	.46

* p<.10, ** p<.05, *** p<.01

Quantitative Tremor

In this overview, analysis was restricted to measures of acceleration and displacement tremor amplitude (RMS and average absolute amplitudes). These quantitative tremor test results did not display statistically significant differences between the mercury-exposed group and the non-exposed group when using the Mann-Whitney test (table 4-5). In the covariance analysis, after adjustment for age, two of the summary measures for the acceleration test were significantly different (acceleration RMS) at the 0.10 level and (acceleration average amplitude) at the 0.05 level. Neither of the displacement measures showed a statistically significant difference between the two groups.

TABLE 4-5
GROUP COMPARISON: Quantitative Tremor Test

Response (mm/s*2)	Exposed N=240 Mean(s.d.)	Non-exposed N=251 Mean(s.d.)	Mann-Whitney Signif	Covariance a Signif
Acc RMS	88.6 (49)	82.0 (32)	.56	.04**
Acc Ave Amplitude	69.5 (41)	63.8 (25)	.51	.03**
Disp RMS	90.7 (30)	90.0 (30)	.81	.83
Disp Ave Amplitude	67.0 (25)	66.2 (25)	.80	.76

* p<.10, ** p<.05, *** p<.01
a. Adjusting for Age(years) and Lead exposure.

Electrodiagnostic Evaluation

The results of the electrodiagnostic evaluation did not show any statistically significant differences between the mercury-exposed group and the non-exposed group on any measures using the Mann-Whitney test and only one significant difference (median sensory amplitude) in the covariance analysis when adjusting for age, height, weight, finger size, and lead exposure (table 4-6, next page).

TABLE 4-6
GROUP COMPARISON: Electrodiagnostic Evaluation

Response	Exposed N=192 Mean(s.d.)	Non-exposed N=191 Mean(s.d.)	Mann-Whitney Signif	Covariance a Signif
Sensory Amplitude (uV)				
Sural	9.1(4.0)	8.8(4.4)	.53	.99
Median	17.2(6.4)	18.0(7.2)	.28	.05**
Ulnar	14.8(6.1)	14.7(5.9)	.79	.97b
Sensory Conduction Velocity (m/s)				
Median	55.6(4.7)	55.3(4.9)	.52	.78
Ulnar	57.3(5.5)	57.7(5.3)	.49	.44
Sensory Distal Latency (ms)				
Sural	3.7(0.3)	3.7(0.4)	.66	.69
Median	3.5(0.5)	3.4(0.4)	.28	.10*
Ulnar	3.4(0.3)	3.4(0.3)	.66	.58
# Sn. Nerves Abnormal	2.17(2.2)	2.07(2.0)	.65	.36
Motor Amplitude (mV)				
Ulnar	10.1(2.0)	10.3(1.8)	.18	.24
Tibial	9.0(3.9)	8.5(3.6)	.21	.20b
Motor Conduction Velocity (m/s)				
Ulnar	57.3(4.6)	57.7(4.7)	.19	.43
Tibial	43.9(4.5)	44.1(4.3)	.47	.39
Motor Distal Latency (ms)				
Ulnar	2.8(0.3)	2.8(0.3)	.70	.87b
Tibial	4.4(0.6)	4.4(0.6)	.98	.89
# Mt. Nerves Abnormal	0.44(.77)	0.46(.75)	.95	.96
sensory:				
Amp % of Normal Mean[c]	49.5(17.2)	50.0(18.0)	.94	.39
CV % of Normal Mean	93.0(10.0)	93.3(10.3)	.72	.61
TM CV % of Normal Mean	91.7 (7.7)	92.1 (7.6)	.73	.44
motor:				
Amp % of Normal Mean	79.9(20.7)	78.3(18.2)	.58	.51b
CV % of Normal Mean	94.4 (7.0)	95.1 (6.9)	.21	.22b
TM CV % of Normal Mean	98.5 (9.2)	98.7 (9.0)	.73	.62

* p<.10, ** p<.05, *** p<.01 TM CV:Terminal Conduction Velocity,
a: Adjusting for age (years), height (inches), weight (lbs.), finger volume (cm sq.), and lead exposure (no, yes).
b: Significant interaction, for differences in coefficients of adjustors.
c: Percent of young adult Normal Mean, not adjusted for age.

Renal Assessment

After standardizing the urinary output per gram of creatinine, none of the urinary measures showed a statistically significant difference between the mercury-exposed group and the non-exposed group (table 4-7).

TABLE 4-7
GROUP COMPARISON: Urinary Results

Response	Exposed N=247 Mean(s.d.)	Non-exposed N=254 Mean(s.d.)	Mann-Whitney Signif	Covariance a Signif
Protein (mg/gm Cre)	78.3 (121.0)	75.4 (162.0)	.10	.19
Albumin (mg/gm Cre)	22.4 (55.3)	24.8 (120.0)	.50	.31
BNAG (umole/gm Cre) b.	1.9 (6.0)	1.5 (3.6)	.52	.23

* p<.10, ** p<.05, *** p<.01
a. Adjusting for Age(years) and Lead exposure.
b. N=486.

Summary

In general, in this overview analysis there were very small differences between the mercury and non-mercury groups. However, the exposed group displayed poorer performance on all of the outcomes observed with a statistically significant difference in nine of the group comparison analyses (table 4-8). Of the variables with p-values less than 0.1 on the covariance analysis, four relate to definite or possible measures of tremor. Acceleration RMS and Acceleration average amplitude are direct measures of tremor while, hand-eye coordination may be adversely affected by a sustention tremor. This is interesting since tremor has long been recognized as a sign of mercury induced nervous system dysfunction. Several of the other test results could reflect peripheral or central nervous system dysfunction, but no clear patterns are evident at this level

of the analysis about which parts of the central nervous system are adversely affected, if any. The presence of the snout reflex is often considered to indicate CNS disease. In both the non-exposed and exposed groups it is quite common. This suggests that it may not be a very reliable indicator of CNS disease but may be related to the aging of the CNS.

TABLE 4-8
Group Comparison: Summary of Significant Findings

Response Variable	Exposed Mean	Non-exposed Mean	Covariance a. Signif.
Quantitative Tremor:			
Acceleration RMS	0.886	0.820	.04
Acceleration Ave. Amplitude	0.695	0.638	.03
Behavioral:			
Reaction Time (msec)	379.5	371.2	.07
Hand-eye (RMS)	8.1	7.2	.004
Neurological Exam:			
Touch Sensation (gms)	3.9	3.8	.09
Proximal strength (% abnormal)	2.4	0.0	.02
Snout reflex (% abnormal)	42.3	34.3	.08
Electrodiagnostic Evaluation:			
Median Sensory Amplitude (uV)	17.2	18.0	.05
Median Sensory Distal Latency (ms)	3.5	3.4	.10

a. Adjusting for Age(years) and Lead exposure.

The reproductive health outcomes are not discussed in this overview chapter but are present in chapter 7 because of different approaches to the analysis of this health outcome.

5. RESULTS OF ALL CLINICAL AND ELECTRODIAGNOSTIC EVALUATIONS

A. Inter-examiner Reproducibility.

Thirty-eight subjects were examined in a crossover design whereby one physician examined approximately half of the subjects first (17 of 38) and the other physician examined the remaining subjects first. There was good agreement for the subjective measures of strength (proximal and distal), sustension tremor, coordination (upper and lower limbs), and muscle stretch reflexes (biceps brachii, brachioradialis, quadriceps, and achilles). Of the nine measures, only the lower extremity coordination measure failed to demonstrate a significant ($p < 0.05$) correlation between examiners. The remaining measures had correlation coefficients ranging from 0.34 to 0.86. Three of the subjective measures demonstrated significant mean differences between examiners. All involved assessment of muscle stretch reflexes with one of the physicians averaging approximately one-half grade higher than the other.

Two of the eleven quantitative measures demonstrated significant mean differences between examiners; two-point discrimination (index finger) and pin-pain sensation (first toe). Like the reflex measurements, both tests demonstrated significant correlation between examiners, with correlation coefficients of $r=0.49$ and 0.33 respectively. The only test that did not demonstrate a significant correlation coefficient between examiners was joint position sensation in the index finger.

The final physicians' clinical impressions regarding the presence or absence of polyneuropathy were compared using a chi-square analysis; the hypothesis that the two examiners were independent in their clinical classifications was rejected ($p < 0.0001$). Their overall agreement rate was 86%.

B. Simple Comparisons Based Upon Mercury Exposure Status.

Five hundred-two subjects were evaluated; 247 were in mercury exposed and 255 were in the control groups. Three hundred-ninety-four subjects had complete electrodiagnostic evaluation; 193 in the mercury exposed and 201 in the control groups. Because the electrodiagnostic tests were both expensive and sensitive, the study plan was limited so that 75% of the subjects had electrodiagnostic tests.

Table 5-1 compares biographical data for the mercury exposed and control subject groups. There were no significant ($p < 0.05$) differences in subject age, height, weight, alcohol consumption, or reported abnormalities, other than a significantly larger proportion of subjects in the mercury exposed than the control group reporting history of malignancy.

TABLE 5-1

Biographical Data for Mercury Exposed and Control Subjects

Characteristic	Mercury Mean (std dev) (n=247)	Control Mean (std dev) (n=255)	p-value[a]
Age (years)	64.1 (7.2)	64.0 (7.2)	.84
Education (years)	11.8 (2.6)	11.8 (2.3)	.98
Height (inches)	70.1 (2.8)	69.6 (2.8)	.43
Weight (pounds)	184.0 (26)	182.0 (29)	.21
Reported alcoholic drinks per week	5.7 (4.5)	6.8 (5.2)	.15
Reported past drinking problem (%)	4.2	2.2	.18
History of malignancy (%)	11.8	6.7 *	.05
Reported hypertension (%)	36.9	42.0	.75
Reported Diabetes (%)	12.4	10.3	.90
Reported tremor (%)	10.0	5.8	.11

* $p < 0.05$

Comparison of all clinical neurologic examination measures for the mercury exposed and control groups demonstrated no significant differences using the Mann-Whitney test before adjustment for age or other potentially important factors. Table 5-2 compares the clinical and quantitative neurologic examination results for the mercury exposed and control groups, before and after excluding subjects with known or suspected medical conditions that could potentially influence the examination. The total group comparison (all subjects) is shown on the left of the table and the restricted group comparison, after the above exclusions, is shown on the right. Only the measures of upper extremity tremor (quantitative) demonstrated significant differences in the covariance analysis after adjustment for age and lead exposure baseline variables. The quantitative tremor measures demonstrated increased tremor in the mercury exposed group compared to the control group. These differences were not significant in the restricted group comparison, although joint position sensation for the foot demonstrated significantly more errors in the mercury exposed than control subjects. This finding was complicated by the existance of significant interaction with the baseline variables. Overall, the few identified statistically significant differences were very small, although mean performance consistently was worse in the mercury exposed than control group for most measures.

The neurologic examination summary results demonstrated no significant differences in the percentage of subjects classified as having a normal examination or definite evidence of a polyneuropathy for the mercury exposed or control subjects, for either the total group or restricted group comparisons (Table 5-3).

TABLE 5-2

Results of the Clinical and Quantitative Neurologic Examination. Comparison of Exposed and Control Subjects Before (Total Group) and After Eliminating Subjects with Neurologic Abnormalities Presumably Unrelated to Mercury Exposure (Restricted Group). Adjusted Means and (S.E.)

	TOTAL GROUP			RESTRICTED GROUP		
Response/Measure	Exposed (n=247)	Control (n=255)	p-value[a]	Exposed (n=193)	Control (n=201)	p-value[a]
STRENGTH:						
Proximal strength (%)[c]	1.89	0.02	.24	0.46	0.02	.38
Distal strength (%)	3.82	1.46	.08	0.88	0.34	.34
Grip strength (Kg)	42.9(.50)	44.0(.49)	.12	43.5(.56)	44.3(.55)	.32
TREMOR:						
Coordination-arms (%)	19.44	14.10	.12	17.15	13.45	.31
Coordination-legs (%)	3.06	2.20	.48	2.54	2.06	.75
Sustention tremor (%)	30.74	24.36	.11	29.72	23.80	.19
Acc Tremor RMS (mm/s*2)	0.86(.02)	0.80(.02)	.04*	0.85(.03)	0.80(.03)	.15
Acc Tremor Ave Amp	0.68(.02)	0.63(.02)	.03*	0.66(.02)	0.62(.02)	.11
SENSATION:						
Joint position (errors/10)						
Hand	.02(.01)	.02(.01)	.66	.02(.009)	.02(.009)	.82
Foot	.29(.06)	.19(.06)	.25b	.20(.04)	.08(.04)	.05b*
Pin-pain, distal/proximal (%)						
Hand	188.0(7.0)	177.7(6.9)	.30	186.6(7.5)	177.2(7.4)	.37
Foot	129.7(5.1)	123.0(5.0)	.35	126.7(5.9)	128.3(5.8)	.31
Two-point discrimination (mm)						
Hand	4.7(.11)	4.4(.11)	.16	4.6(.12)	4.4(.12)	.20
Foot	34.3(.92)	32.4(.91)	.14b	32.0(.77)	31.8(.75)	.82
Touch-pressure (log mg)						
Hand	3.6(.02)	3.5(.02)	.09	3.6(.03)	3.5(.03)	.52
Foot	3.9(.03)	3.8(.03)	.12b	3.8(.03)	3.8(.03)	.42b
Vibration (seconds)						
Hand	8.5(.18)	8.2(.18)	.24	8.4(.20)	8.1(.20)	.22
Foot	16.0(.28)	15.5(.28)	.24	15.6(.31)	15.1(.30)	.27
REFLEXES:						
Muscle Stretch reflexes:						
Biceps	1.9(.05)	1.9(.05)	.99	1.9(.06)	2.0(.06)	.30
Brachioradialis	1.9(.05)	1.8(.05)	.98	1.9(.06)	1.9(.06)	.56
Quadriceps	2.3(.05)	2.3(.05)	.80	2.3(.05)	2.3(.05)	.87
Achilles	1.7(.06)	1.6(.06)	.28	1.8(.06)	1.9(.06)	.20
Pathologic Reflexes:						
Babinski (%)	3.7	1.6	.16	3.1	1.0	.16
Jaw (%)	7.4	5.8	.44	7.5	6.9	.78
Snout(%)	44.3	36.2	.07	39.4	35.4	.44

* $p < .05$, ** $p < .01$

a. Quantitative outcomes: covariance analysis: test for difference in adjusted means, adjusting for age (years) and lead exposure (no, yes). Percents: Logistic regression analysis to adjust for age (years) and lead exposure (no, yes).

b. Significant interaction, for differences in coefficients of adjustors.

c. Positive indicates presence of abnormal condition for all percentile scores except pin-pain (parametric measure).

TABLE 5-3

Results of the Neurologic Examination Summary. Comparison of Exposed and Control Subjects, Before (Total Group) and After Eliminating Subjects with Neurologic Abnormalities Presumably Unrelated to Mercury Exposure (Restricted Group). Adjusted Percents by Logistic Regression Analysis.

	TOTAL GROUP			RESTRICTED GROUP		
	Exposed (n=247)	Control (n=255)		Exposed (n=193)	Control (n=201)	
Response	Percent-Positive		p-value[a]	Percent-Positive		p-value[a]
Normal Examination	50.2	53.4	.55	54.6	58.8	.45
Polyneuropathy	10.0	11.7	.48	5.5	7.8	.29

* $p < .05$, ** $p < .01$

a. Difference between adjusted percents using Logistic regression analysis to adjust for age (years) and lead exposure (no, yes).

Note: Subjects with normal examination had no evidence of polyneuropathy or any other neurologic abnormality. Only subjects with unequivocal clinial evidence of polyneuropathy were included in the polyneuropathy group.

The results of the electrodiagnostic evaluation comparing mercury exposed and control subjects before and after restriction are shown in Table 5-4. There were no statistically significant differences between the mercury exposed and control groups on any measures using the Mann-Whitney test and only one significant difference (median sensory amplitude) in the covariance analysis for the a total group, after adjusting for age, height, weight, finger size, and lead exposure. This difference was not significant in the restricted group analysis.

TABLE 5-4

**Results of the Electrodiagnostic Evaluation.
Comparison of Mercury and Control Subjects, Before (Total Group) and After Eliminating Subjects with Neurologic Abnormalities Presumably Unrelated to Mercury Exposure (Restricted Group). Adjusted Means and (S.E.)**

	TOTAL GROUP			RESTRICTED GROUP		
RESPONSE	Exposed (n=192)	Control (n=191)	p-value[a]	Exposed (n=155)	Control (n=150)	p-value[a]
Sensory Amplitude (uV)						
Sural	9.0(.28)	9.0(.28)	.99	9.2(.30)	9.4(.31)	.66
Median	17.0(.43)	18.2(.44)	.05*	17.3(.47)	18.4(.48)	.09
Ulnar	14.7(.40)	14.7(.40)	.97b	14.9(.43)	15.1(.43)	.74
Sensory Nerve Conduction Velocity (m/s)						
Median	55.5(.34)	55.4(.34)	.78	55.8(.36)	55.8(.37)	.86
Ulnar	57.3(.38)	57.7(.38)	.44	57.7(.38)	58.2(.39)	.36
Sensory Distal latency (ms)						
Sural	3.7(.02)	3.7(.02)	.69	3.6(.03)	3.7(.03)	.56
Median	3.5(.03)	3.4(.03)	.10	3.4(.03)	3.4(.03)	.36
Ulnar	3.4(.02)	3.4(.02)	.58	3.4(.02)	3.4(.02)	.72
# Sensory Nerve Abnormalities	2.2(.14)	2.0(.14)	.36	1.9(.14)	1.8(.14)	.62
Motor Amplitude (mV)						
Ulnar	10.1(.14)	10.3(.14)	.24	10.1(.15)	10.4(.16)	.14
Tibial	9.0(.25)	8.5(.25)	.20b	9.0(.28)	8.5(.28)	.21
Motor Conduction Velocity (m/s)						
Ulnar	57.3(.33)	57.7(.33)	.43	57.8(.35)	58.0(.36)	.78b
Tibial	43.8(.31)	44.2(.31)	.39	44.2(.31)	44.5(.31)	.61
Motor Distal Latency (ms)						
Ulnar	2.8(.02)	2.8(.02)	.87b	2.8(.02)	2.8(.02)	.96
Tibial	4.4(.04)	4.4(.04)	.89	4.5(.04)	4.4(.04)	.55
# Motor Nerve Abnormalities	0.44(.05)	0.45(.05)	.96	0.34(.05)	0.38(.06)	.67
SENSORY						
Amp % of Normal Mean[c]	49.0(1.1)	50.0(1.1)	.39	50.2(1.1)	51.8(1.1)	.31
CV % of Normal Mean	92.9(.70)	93.4(.70)	.61	94.1(.53)	94.6(.54)	.49
TMCV % of Normal Mean	91.6(.53)	92.2(.53)	.44	92.4(.56)	92.7(.56)	.83
MOTOR						
Amp % of Normal Mean	79.8(1.3)	78.6(1.3)	.51b	80.0(1.4)	79.0(1.4)	.63
CV % of Normal Mean	94.4(.48)	95.2(.48)	.22b	95.3(.50)	95.7(.51)	.57b
TMCV % of Normal Mean	98.4(.63)	98.8(.63)	.62	98.7(.69)	99.4(.70)	.50

* $p < .05$, ** $p < .01$

Amp = Amplitude; CV = Conduction velocity; TMCV = Terminal Conduction Velocity.

a. Covariance analysis: adjusting for age (years), lead exposure (no, yes), height (inches), weight (lbs.) and finger volume (cc).

b. Significant interaction for differences in coefficients of adjustors.

c. Percent of young adult normal mean, not adjusted for age.

C. Regression Analysis.

Multiple linear regression analysis was used to correct for effects of potentially important covariates and to further investigate the relationship between subjects' urine mercury history variables and their clinical and electrodiagnostic findings. Stepwise forward regression analysis was used to identify covariates that had a significant influence upon examination measures. Analysis was performed on the total group (all subjects) and on the restricted group (after eliminating subjects with known or suspected medical conditions). Significant covariates for the clinical examination included age and the presence or absence of prior lead exposure (when $p < .10$), the same covariates identified apriori as the baseline variables used in the initial simple comparisons based upon exposure status. Significant covariates for the electrodiagnostic evaluation included age, height, weight, finger volume, and the presence or absence of lead exposure.

These variables were used as covariates in subsequent regression analyses for the clinical and electrodiagnostic evaluations respectively. Variables that did not have a significant association were not included in further regression analyses. These variables included all of the alcohol consumption variables obtained from the questionnaire and interview and other occupational exposure variables obtained from the above sources and work related exposure records. In the total group analyses, adjustment was made for the 10 identified exclusion categories (connective tissue disorder, inflammatory, metabolic, neoplasm, nutritional, psychiatric, structural, toxic or medication exposure, trauma, vascular). Subjects identified as having neurologic abnormalities presumably unrelated to

mercury exposure but having an indeterminant etiology (e.g., myelopathy) were included in the analysis without adjustment.

Table 5-5 summarizes the results of the regression analysis for the total group. Similar results were found for the restricted group analysis. The partial correlation coefficients for two of the urine mercury history variables and the clinical examination measures are shown. The two urine mercury history variables used were the cumulative urine mercury and the peak urine mercury level (highest urine level for the individual subject). There were consistently positive correlations between declining neurologic performance and increasing mercury exposure. For the purpose of regression analysis, the clinical variables rated on a 5-point scale were treated as continuous measures. Significant regression coefficients were identified for several measures including strength (proximal and distal), tremor (sustension and quantitative), sensation (joint position sensation/foot, two-point discrimination/hand, touch-pressure/foot, and vibration/foot). Relatively good agreement existed between the two urine mercury history variables, although a greater number of significant coefficients existed using the peak urine mercury measure. These findings suggest a weak (small partial correlation coefficients) but significant dose-response relationship between abnormal neurologic function and increasing level of mercury exposure.

There was the possibility that only two or three subjects were responsible for several of the significant regression relationships between the cumulative and peak urine mercury history variables and the neurologic findings. Visual analysis of bivariate scatter diagrams for all of the statistically significant relationships recorded in Table 5-5 was used to identify subjects with the worst performance. Several of the regression

TABLE 5-5

Dose-response Analysis: Summary of Regression Analyses of Urine Mercury History Variables and Results of the Clinical and Quantitative Neurologic Examination, After Adjusting for Baseline Variables and Ten Exclusion Categories

Variable	Cumulative Urine Mercury Regression (n=502) Partial Corr	p-value[a]	Peak Urine Mercury Regression (n=502) Partial Corr	p-value[a]
MOTOR EXAMINATION:				
STRENGTH:				
Proximal strength	.10	.04*	.10	.02*
Distal strength	.08	.07	.13	<.01**
Grip strength	-.02	.63	-.02	.57
TREMOR:				
Coordination-arms	.10	.02*	.08	.07
Coordination-legs	.01	.85	<.01	.94
Sustention tremor	.06	.15	.10	.04*
Acc Tremor RMS (mm/s*2)	.10	.03*	.15	<.001***
Acc Tremor Ave Amplitude	.11	.02*	.16	<.001***
SENSORY EXAMINATION:				
Joint position				
Hand	.04	.38	-.01	.89
Foot	.07	.11	.09	.05*
Pin-pain, distal/proximal				
Hand	.02	.58	.04	.32
Foot	-.01	.82	.02	.66
Two-point discrimination				
Hand	.14	<.01**	.05	.27
Foot	.07	.13	.09	.06
Touch-pressure				
Hand	.05	.24	.05	.27
Foot	.11	.02*	.16	<.001***
Vibration				
Hand	.04	.44	.05	.28
Foot	.04	.39	.10	.03*
REFLEX EXAMINATION:				
Muscle stretch reflexes				
Biceps	.01	.78	-.03	.56
Brachii	.01	.84	-.06	.22
Quadriceps	.01	.84	-.02	.68
Achilles	.03	.54	-.05	.30

* $p < .05$, ** $p < .01$, *** $p < .001$

a. Adjusting for age (years), lead exposure (no, yes) and known clinical abnormality categories (no, yes).

lines were influenced substantially by a small number of subjects. Specifically, dose-response relationships between measures of coordination, sustension tremor, and touch-pressure sensation (hand), and vibration sensation, and the cumulative and peak urine mercury measures were no longer significant after removing no more than three subjects. Similar influence by a small number of subjects was not demonstrated for the measures of strength, or joint position and touch-pressure sensation for the foot.

Results of the multiple regression analysis between electrodiagnostic findings and two of the urine mercury history variables are shown in Table 5-6. No significant dose-response relationships were identified for any of the measures and the cumulative urine mercury measure, although the total number of sensory and motor nerve abnormalities approached statistical significance ($p=0.07$ and 0.06, respectively). Statistically significant regression coefficients were identified for the median sensory distal latency and the total number of motor nerve abnormalities using the peak urine mercury variable.

D. Selective Evaluation of Subjects with High Mercury Exposure.

Because of the suggested dose-response relationships described above, subjects were divided into two groups: those who had one or more urine mercury peaks above 0.6 mg/L (n=112) and those without a history of such peaks (n=390). This exposure level was chosen because of its conventional use as a measure of substantial exposure. For most response measures, mean neurologic performance was worse and the presence of neurologic abnormalities more common in the higher mercury exposure group (Table 5-7). Significant ($p < 0.05$) differences existed in tests of strength (proximal and distal), coordination (legs), sustension tremor, quantitative tremor,

TABLE 5-6

Dose-response Analysis: Summary of Regression Analyses of Urine Mercury History Variables and Electrodiagnostic Evaluation After Adjusting for Baseline Variables and Ten Exclusion Categories

Variable	Cumulative Urine Mercury Regression (n=383) Partial Corr	p-value[a]	Peak Urine Mercury Regression (n=383) Partial Corr	p-value[a]
Sensory Amplitude (uV)				
Sural	-.02	.64	-.01	.87
Median	-.08	.12	-.06	.24
Ulnar	-.03	.50	-.02	.74
Sensory Conduction Velocity (m/s)				
Median	.02	.72	.04	.48
Ulnar	-.02	.74	-.01	.79
Sensory Distal Latency (ms)				
Sural	-.02	.75	-.08	.15
Median	.09	.09	.11	.04*
Ulnar	.07	.16	.07	.18
# Sensory Nerve Abnormalities	.10	.07	.06	.24
Motor Amplitude (mV)				
Ulnar	-.06	.21	-.03	.52
Tibial	.08	.14	.04	.42
Motor Conduction Velocity				
Ulnar	-.05	.36	-.09	.08
Tibial	-.01	.88	-.01	.92
Motor Distal Latency (ms)				
Ulnar	-.01	.81	-.02	.67
Tibial	-.05	.30	-.09	.09
# Motor Nerve Abnormalities	.10	.06	.11	.03*
SENSORY				
Amp % of normal mean[b]	-.06	.22	-.04	.47
CV % of normal mean	-.02	.75	<.01	.98
TMCV % of normal mean	-.06	.24	-.06	.26
MOTOR				
Amp % of normal mean	.03	.52	.01	.82
CV % of normal mean	-.05	.36	-.06	.24
TMCV % of normal mean	.01	.86	<.01	.99

* $p < .05$, ** $p < .01$

a. Adjusting for age (years), lead exposure (no, yes) height (inches), weight (pounds), and known clinical abnormality categories (no,yes).

b. Amp = Amplitude; DL = Distal Latency; CV = Conduction Velocity, TMCV = Terminal Conduction Velocity.

TABLE 5-7

Results of the Clinical and Quantitative Neurologic Examination. Comparison of Subjects with One or More Urine Mercury Peaks > 0.6 mg/L to Subjects without Such Peaks. Adjusted Means and (S.E.).

	TOTAL GROUP			URINE MERCURY PEAK > 0.6 mg/L		
Response/Measure	Exposed (n=247)	Control (n=255)	p-value[a]	Yes (n=112)	No (n=390)	p-value[a]
STRENGTH:						
Proximal strength (%)[c]	1.89	0.02	.24	3.11	0.04	.02*
Distal strength (%)	3.82	1.46	.08	6.04	1.77	.01**
Grip strength (Kg)	42.9(.50)	44.0(.49)	.12	43.4(.74)	43.5(.40)	.94
TREMOR:						
Coordination-arms (%)	19.44	14.10	.12	22.95	15.18	.07
Coordination-legs (%)	3.06	2.20	.48	5.33	1.90	.04*
Sustention tremor (%)	30.74	24.36	.11	35.24	25.56	.05*
Acc Tremor RMS (mm/s*2)	0.86(.02)	0.80(.02)	.04*	0.94(.04)	0.80(.02)	.002**
Acc Tremor Ave Amp	0.68(.02)	0.63(.02)	.03*	0.74(.03)	0.63(.02)	.001**
SENSATION:						
Joint position (#/10)						
Hand	.02(.01)	.02(.01)	.66	.01(.01)	.02(.02)	.41
Foot	.29(.06)	.19(.06)	.25b	.38(.09)	.20(.05)	.09b
Pin-pain, distal/proximal (%)						
Hand	188.0(7.0)	177.7(6.9)	.30	183.4(10.4)	182.6(5.6)	.95
Foot	129.7(5.1)	123.0(5.0)	.35	127.8(7.6)	125.9(4.0)	.82
Two-point discrimination (mm)						
Hand	4.7(.11)	4.4(.11)	.16	4.9(.16)	4.5(.09)	.04*
Foot	34.3(.92)	32.4(.91)	.14b	33.9(1.4)	33.2(0.7)	.65
Touch-pressure (log mg)						
Hand	3.6(.02)	3.5(.02)	.09	3.6(.04)	3.6(.02)	.33
Foot	3.9(.03)	3.8(.03)	.12b	4.0(.04)	3.8(.02)	.01b**
Vibration (seconds)						
Hand	8.5(.18)	8.2(.18)	.24	8.6(.26)	8.3(.14)	.30
Foot	16.0(.28)	15.5(.28)	.24	16.3(.42)	15.6(.22)	.14
REFLEXES:						
Muscle Stretch reflexes:						
Biceps	1.9(.05)	1.9(.05)	.99	2.0(.08)	2.0(.04)	.85
Brachioradialis	1.9(.05)	1.8(.05)	.98	1.8(.08)	1.9(.04)	.47
Quadriceps	2.3(.05)	2.3(.05)	.80	2.3(.08)	2.2(.04)	.69
Achilles	1.7(.06)	1.6(.06)	.28	1.6(.08)	1.7(.05)	.20
Pathologic Reflexes:						
Babinski (%)	3.7	1.6	.16	5.7	1.9	.04*
Jaw (%)	7.4	5.8	.44	9.1	5.8	.19
Snout(%)	44.3	36.2	.07	49.5	37.8	.03*

* $p < .05$, ** $p < .01$, *** $p < .001$

a. Covariance analysis was used for parametric data: test for difference in adjusted means, adjusting for age (years) and lead exposure (no, yes). Percents: Logistic regression analysis to adjust for age (years and lead exposure (no, yes).

b. Significant interaction, for differences in coefficients of adjustors.

c. Positive indicates presence of abnormal condition for all percentile scores except pin-pain (parametric measure).

two-point discrimination (hand), touch-pressure sensation (foot), Babinski response, and snout reflex. The percentage of subjects with abnormal coordination in the arms and the number of errors in joint position testing of the foot were higher in the mercury exposed group, approaching clinical significance (p=0.07 and 0.09 respectively). Neurologic examination summary results are shown in Table 5-8 for the total and restricted groups. A significantly lower percentage of subjects in the mercury exposed group had a normal neurologic examination, although this difference could not be attributed only to the presence or absence of clinical polyneuropathy.

To further evaluate the possible relationship between the presence of clinical polyneuropathy and mercury exposure, we divided exposed subjects into three groups based upon the urine mercury peak values. The percentage of subjects with clinical polyneuropathy was highest in subjects with peaks above 0.7 mg/L (20% versus 10%). We then subdivided the highest group into

TABLE 5-8

Results of the Neurologic Examination Summary. Comparison of Subjects with One or More Urine Mercury Peaks > 0.6 mg/L to Subjects Without Such Peaks. Adjusted Percents by Logistic Regression Analysis.

	TOTAL GROUP			URINE MERCURY PEAK > 0.6 mg/L		
	Exposed (n=247)	Control (n=255)		Yes (n=112)	No (n=390)	
RESPONSE	Percent-Positive		p-value[a]	Percent-Positive		p-value[a]
Normal examination	50.2	53.4	.55	42.6	54.4	.05*
Polyneuropathy	10.0	11.7	.48	12.9	10.2	.38

* $p < .05$, ** $p < .01$

a. Difference between adjusted percents using Logistic regression analysis to adjust for age (years) and lead exposure (no, yes).

Note: Subjects with normal examination had no evidence of polyneuropathy or any other neurologic abnormality. Only subjects with unequivocal clinical evidence of polyneuropathy were included in the polyneuropathy group.

two approximately equal groups. In the highest exposure group, (urine mercury peak above 0.85 mg/L) 28% of subjects had clinical evidence of polyneuropathy (Table 5-8A). By comparison, only 10% of subjects who never had a urine mercury peak above 0.85 mg/L had clinical polyneuropathy (X2; p=0.005). Multiple logistic regression analysis suggested that subjects with a urine mercury peak above 0.85 mg/L had approximately a two to three-fold increased risk of having a clinically detectable polyneuropathy after adjusting for potential confounding factors of age, presence of diabetes mellitus, history of lead exposure, reported drinking problem, and presence of co-existing illnesses (Table 5-8B).

Results of the electrodiagnostic examination were compared for subjects with one or more urine mercury peaks above 0.6 mg/L (n=95) to subjects without such peaks (n=291). The only statistically significant difference was a slightly prolonged median sensory distal latency in the higher compared to the lower exposure group (Table 5-9). The mean difference of 1 ms was of questionable clinical significance and the magnitude of other differences were equally small. Further subdivision of mercury exposed subjects into groups of two or more urine mercury peaks above 0.6 mg/L (n=27) to those without (n=307) demonstrated a significantly increased number of sensory and motor nerve abnormalities in the higher compared to the lower exposure group (p=0.04 and p = 0.005, respectively). Using three or more urine mercury peaks above 0.6 mg/L (n=15), the number of motor nerve abnormalities again was significantly higher in the higher exposure group (p=0.001), although the number of sensory nerve abnormalities was no longer significantly different between groups (Table 5-9A). Similar results were obtained using the restricted group.

TABLE 5-8A

Results of the Neurologic Examination Summary. Comparison for Different Peak Urine Mercury History Levels in Mercury Exposed Subjects.

Response	Total Mercury Group (n=247) Urinary Mercury Peak Levels (ug/L) < 0.45 (n=86)	0.45-0.69 (n=77)	0.70-0.85 (n=33)	> 0.85 (n=51)
Normal (%)	73 .3	75.3	72.7	56.9
Equivocal Polyneuropathy (%)	14.0	16.9	18.2	15.7
Polyneuropathy (%)	12.8	7.8	9.1	27.5 a **

* $p <_2 .05$, ** $p < .01$
a. X^2 analysis; subjects with peak level above 0.85 mg/L vs. remaining subjects
Note: Subjects with normal examination had no evidence of polyneuropathy or any other neurologic abnormality.

TABLE 5-8B

Predictors of Clinical Polyneuropathy
Logistic Regression Analysis

Independent Variable	Beta	SE	Signif.	Estimated Odds Ratio
Urine Mercury History Peak Above 0.85 mg/L	1.01	.47	.03	2.8
Age (years)	.17	.23	<.001	1.2
Reported Alcohol	.33	.73	.65	1.4
Reported Lead Exposure	.52	.32	.11	1.7
Cancer [a]	1.44	.99	.15	4.2
Medications [b]	1.45	.85	.09	4.3
Diabetes [a]	2.74	.48	<.001	15.5

Summary of logistic regression model:

Intercept only: -2 Log Likelihood = 385.28
Model: -2 Log Likelihood = 267.13
Model Chi-square (7 d.f.) = 118.15 ($p < 0.0001$)

Predicting definite polyneuropathy vs. no polyneuropathy.
Beta = log odds ratio.
a. From medical history as evaluated by Neurologist (no, yes).
b. Dapsone, theophylline, or valium.

These individual comparisons may be summarized in an overall test for trend in increasing number of sensory and motor nerve abnormalities with increasing number of urine mercury peaks > 0.6 mg/L. This test was significant for both the number of sensory and motor nerve abnormalities (p=.04 and p=.001). This trend was also significant in the restricted group analysis.

TABLE 5-9

Results of the Electrodiagnostic Examination. Comparison of Subjects with One or More Urine Mercury Peaks > 0.6 mg/L to Subjects Without Such Peaks. Adjusted Means and (S.E.)

	TOTAL GROUP			URINE MERCURY PEAK >0.6 mg/L		
RESPONSE	Exposed (n=192)	Control (n=191)	p-value[a]	Yes (n=95)	No (n=291)	p-value[a]
Sensory Amplitude (uV)						
Sural	9.0(.28)	9.0(.28)	.99	9.0(.40)	9.0(.22)	.93
Median	17.0(.43)	18.2(.44)	.05*	17.0(.63)	17.8(.35)	.31
Ulnar	14.7(.40)	14.7(.40)	.97b	14.3(.57)	14.9(.32)	.43
Sensory Nerve Conduction Velocity (m/s)						
Median	55.5(.34)	55.4(.34)	.78	55.6(.49)	55.5(.27)	.68
Ulnar	57.3(.38)	57.7(.38)	.44	57.0(.55)	57.6(.30)	.29
Sensory Distal latency (ms)						
Sural	3.7(.02)	3.7(.02)	.69	3.7(.04)	3.7(.02)	.49
Median	3.5(.03)	3.4(.03)	.10	3.5(.04)	3.4(.02)	.03*
Ulnar	3.4(.02)	3.4(.02)	.58	3.4(.03)	3.4(.02)	.09
# Sensory Nerves Abnormalities	2.2(.14)	2.0(.14)	.36	2.3(.20)	2.0(.12)	.21
Motor Amplitude (mV)						
Ulnar	10.1(.14)	10.3(.14)	.24	10.2(.20)	10.2(.11)	.93
Tibial	9.0(.25)	8.5(.25)	.20b	9.0(.37)	8.7(.21)	.53
Motor Conduction Velocity (m/s)						
Ulnar	57.3(.33)	57.7(.33)	.43	56.7(.48)	57.8(.27)	.06
Tibial	43.8(.31)	44.2(.31)	.39	44.1(.04)	44.0(.25)	.89
Motor Distal Latency (ms)						
Ulnar	2.8(.02)	2.8(.02)	.87b	2.8(.03)	2.8(.02)	.99
Tibial	4.4(.04)	4.4(.04)	.89	4.4(.06)	4.5(.03)	.28
# Motor Nerve Abnormalities	0.44(.05)	0.45(.05)	.96	0.56(.08)	0.41(.04)	.08
SENSORY						
Amp % of Normal Mean [c]	49.0(1.1)	50.0(1.1)	.39	48.3(1.5)	50.2(.88)	.30
CV % of Normal Mean	92.9(.70)	93.4(.70)	.61	92.2(1.0)	93.4(.57)	.27
TMCV % of Normal Mean	91.6(.53)	92.2(.53)	.44	90.8(.75)	92.2(.43)	.10
MOTOR						
Amp % of Normal Mean	79.8(1.3)	78.6(1.3)	51b	79.7(1.9)	79.0(1.1)	.76
CV % of Normal Mean	94.4(.48)	95.2(.48)	.22b	94.0(.69)	95.0(.39)	.21
TMCV % of Normal Mean	98.4(.63)	98.8(.63)	.62	98.7(.90)	98.5(.51)	.89

* p < .05, ** p < .01

Amp = Amplitude; CV = Conduction velocity; TMCV = Terminal Conduction Velocity

a. Covariance analysis: adjusting for age (years), lead exposure (no, yes) ,height (inches), weight (lbs.), and finger volume (cc.).

b. Significant interaction, for differences in coefficients of adjustors.

c. Percent of young adult normal mean, not adjusted for age.

TABLE 5-9A

Results of the Electrodiagnostic Examination
Number of Sensory and Motor Nerve Abnormalities vs.
Number of Urine Mercury Peaks Above 0.6 mg/L

	TOTAL GROUP			RESTRICTED GROUP		
No. of Urine Mercury Peaks Above 0.6 mg/L	No. of Subjects	No. of Sensory Abnormalities	No. of Motor Abnormalities	No. of Subjects	No. of Sensory Abnormalities	No. of Motor Abnormalities
0	291	2.0	0.4*a	231	1.9	0.3a
1	56	2.2	0.5**b	49	1.8	0.4**b
2	24	2.5	0.5***c	19	2.3	0.6*c
3	12	2.8	0.8***d	7	2.6	0.9d
4	3	3.5	2.3	1	2.0	1.0

* $p < .05$, ** $< .01$, *** $p < .001$
a. Test of subjects in line 0 (0 peaks above 0.6 mg/L) vs. those in lines 1-4; Student t test.
b. Test of subjects in lines 0 and 1 vs. those in lines 2-4.
c. Test of subjects in lines 0-2 vs. those in lines 3-4.
d. Test of subjects in lines 0-3 vs. those in line 4.

E. Age and Exposure Interaction.

The regression analysis described above demonstrated a significant trend toward decreasing neurologic performance and increasing age. Because of this, we further evaluated this relationship for measures that had demonstrated either a significant correlation with increasing mercury exposure or significant selective differences between high vs. low level exposed subjects. Included were measures of strength, tremor, two-point discrimination, touch-pressure sensation, vibration sensation, and the presence of a snout reflex. The clinical summary variable for the presence or absence of polyneuropathy also was evaluated, as were the sensory and

motor electrodiagnostic summary variables (number of sensory or motor nerve abnormalities). In the absence of known mercury exposure, most of the measures demonstrated poorer performance with increasing age. Of greater interest, several measures showed a much more pronounced trend toward deteriorating performance following mercury exposure and advancing age. This trend was examined for the two measures of mercury exposure used in the previous regression analyses (cumulative urine mercury and peak urine mercury level). Interaction between age and mercury exposure was determined by including a variable in the regression equation defined as the product of the subject's age and level of exposure. A significant partial correlation coefficient for this variable indicated an age-mercury interaction.

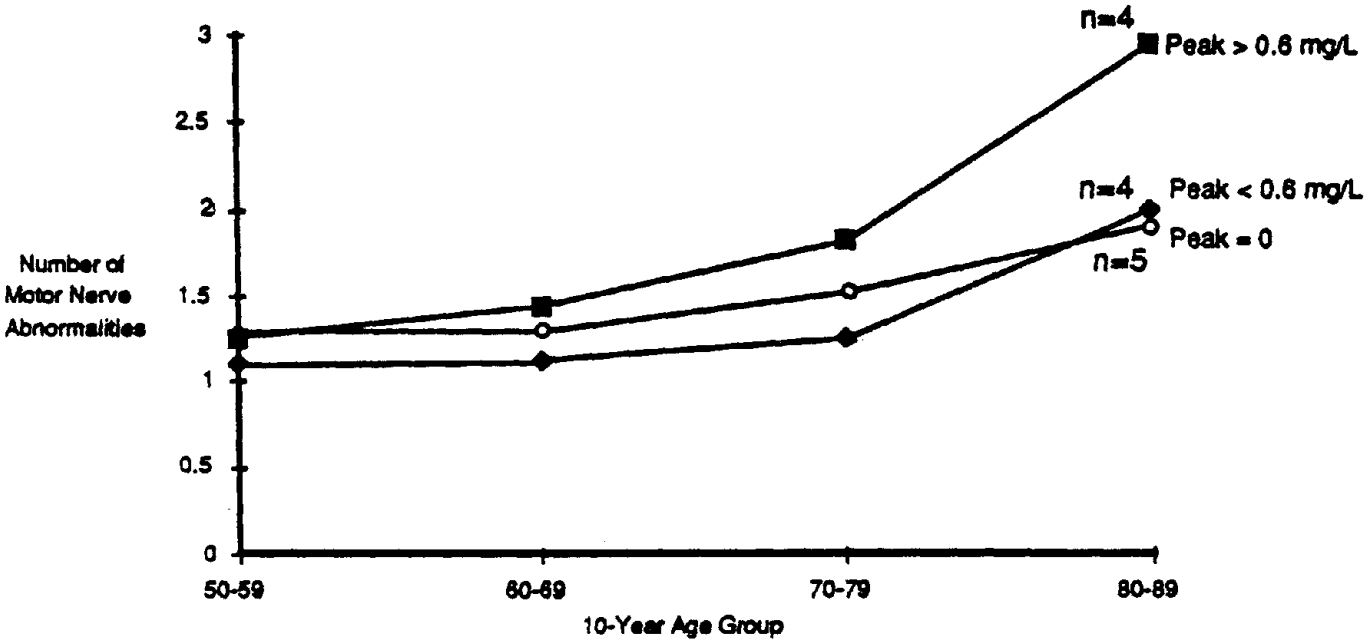
Six outcome measures from the neurologic and electrodiagnostic examinations had a significant age-cumulative mercury interaction. Included were proximal and distal strength, tremor (acceleration RMS and average amplitude), touch-pressure sensation (foot), and vibration sensation (foot). These four measures plus three additional measures (two-point discrimination, hand and foot; number of motor nerve abnormalities) were found to have a significant age-peak mercury interaction. The averaged number of motor nerve abnormalities as a function of age (by decade) are shown for control subjects and subjects with two levels of mercury exposure (peak > 0.6 mg/L, peak < 0.6 mg/L) in Figure 1. This figure is representative of the other outcome measures showing a significant age-peak mercury interaction. In the figure, only subjects 80 to 89 years of age demonstrated significant differences between high exposure versus low exposure or control subjects. The neurologic

examination summary result for the presence or absence of polyneuropathy did not demonstrate a significant age-mercury interaction for either the cumulative or peak mercury measures.

Similar comparison of urine mercury history variables (discussed elsewhere) demonstrated that exposure was not significantly different between the younger and older exposed subjects. There is neither a trend toward higher peak or duration exposures in the older subjects.

FIGURE 5-1

Demonstration of Age-Mercury Interaction: Average Number of Motor Nerve Abnormalities as a Function of Age (Decade) for Control Subjects and Subjects with Two Levels of Mercury Exposure



F. Urine Mercury Comparison For Abnormal and Normal Exposed Subjects.

If clinical or electrodiagnostic abnormalities were related to the magnitude of prior mercury exposure and present only in subjects having the highest exposure, comparison of mercury indexes for "abnormal" and "normal" exposed subjects might be a more sensitive measure than simple group comparisons for identifying such an effect. If many of the exposed subjects had only low exposure levels, they would tend to dilute abnormalities in the mercury exposed group. Because the dose-response studies suggested a weak but significant relationship between tremor and several tests of sensation, subjects were divided into groups having abnormal tremor or evidence of polyneuropathy (based upon clinical and electrodiagnostic criteria). These subjects were compared to the mercury exposed subjects having neither abnormal tremor or evidence of polyneuropathy.

A detailed analysis of the results of the tremor measures is recorded elsewhere (Chapter 6). That evaluation demonstrated that the neurologists were consistent in confirming the quantitative tremor measurement results. Of the 10 mercury exposed subjects with quantitative tremor amplitudes exceeding the upper 95% confidence limit, 9 were identified as having clinically abnormal tremor. Because slightly different exclusion criteria were used in the separate tremor evaluation, the results demonstrate minor differences.

Urine mercury history variables from exposed subjects with clinical evidence of abnormal tremor (equal to or greater than "trace") from both the total and restricted groups were compared to results from exposed subjects with a normal clinical tremor examination (Table 5-10). Subjects with abnormal tremor from the total group had significantly higher urine

mercury peak levels than subjects without evidence of tremor. Although the analysis for the restricted group was of similar magnitude and in the same direction, the difference was only marginally significant (p=.08). None of the other urine mercury history variables was significantly different. Because subjects with "trace" tremor were defined as abnormal, a large proportion of subjects were identified as having clinically abnormal tremor. However, analyses stratifying the subjects into groups with unequivocally abnormal tremor did not demonstrate any further differences in urine mercury history variables.

TABLE 5-10

Comparison of Urine Mercury History Variables for Subjects with and Without Clinical Evidence of Abnormal Sustension Tremor (Total and Restricted Groups). Means and (std dev)

	TOTAL GROUP Abnormal Sustension Tremor			RESTRICTED GROUP Abnormal Sustension Tremor		
URINE MERCURY HISTORY VARIABLES	Yes (n=84)	No (n=163)	p value[a]	Yes (n=65)	No (n=128)	p value[a]
Cumulative Urine Mercury (Sum of average quarterly values, ug/L)	3527 (1238)	3630 (1168)	.52	3511 (1128)	3587 (1109)	.65
Duration of Exposure (quarters)	20.4 (8.4)	21.4 (9.1)	.38	20.4 (7.9)	21.8 (9.1)	.27
Peak Levels above 0.3 mg/L in Entire History (number)	3.6 (2.5)	3.5 (2.5)	.94	3.4 (2.4)	3.4 (2.5)	.93
Peak Levels above 0.6 mg/L in Entire History (number)	0.8 (1.0)	0.7 (1.0)	.27	0.7 (0.9)	0.7 (0.9)	.79
Peak Level (Highest Level in Entire History, ug/L)	717 (481)	611 (291)	.03*	691 (438)	601 (281)	.08
Average Urine Mercury, 1955-1956 (ug/L)	265 (138)	269 (129)	.81	266 (128)	258 (124)	.70

* $p < .05$, ** $p < .01$
a. Student t test.

Results of the comparison between subjects with clinical and electrodiagnostic evidence of polyneuropathy to subjects without such abnormalities are shown in Table 5-11. Mercury exposed subjects with clinical evidence of polyneuropathy from both the total and restricted groups had significantly higher urine mercury peak levels than subjects with normal neurologic examinations. Although the mercury exposure levels were not normally distributed between the groups, similar results were obtained using the Mann-Whitney test. The number of recorded urine mercury peaks exceeding 0.6 mg/L also was significantly higher for subjects with than those without polyneuropathy in the total group, but this difference, while in the same direction, was not significant in the restricted group. All of the urine mercury history variables except duration of exposure were greater for subjects with than without polyneuropathy. Urine mercury history variables for subjects having clinical evidence of polyneuropathy plus electrodiagnostic confirmation were compared to mercury exposed subjects having neither clinic or electrodiagnostic evidence of polyneuropathy. Results similar to those described above were found for this smaller group of subjects. Three of the six urinary mercury history variables demonstrated significantly higher mercury exposure in the 16 subjects with polyneuropathy compared to mercury exposed subjects with normal examinations. The urine mercury history variables included cumulative urine mercury, the number of urine mercury peaks above 0.3 mg/L, and the peak level (highest urine mercury level recorded). Two of the remaining three measures were higher in the polyneuropathy group, but not significantly so. The only index that was not higher was the duration of exposure. For the restricted group, only the number of peak levels above 0.3 mg/L was significantly higher in subjects with clinical and

TABLE 5-11

Comparison of Urine Mercury History Variables for Subjects with Clinical and Electrodiagnostic Evidence of Polyneuropathy versus Subjects with Normal Clinical and Electrodiagnostic Evaluation (Total and Restricted Groups). Means and (std dev)

Urine Mercury History Variables	TOTAL GROUP Normal (n=174)	Clinical Polyneuropathy (n=34)	p-value[a]	Clinical & EMG Polyneuropathy (n=16)	p-value[a]	RESTRICTED GROUP Normal (n=148)	Clinical Polyneuropathy (n=18)	p-value[a]	Clinical & EMG Polyneuropathy (n=7)	p-value[a]
Cumulative urine (Sum of average quarterly values, ug/L)	3480 (1104)	3888 (1570)	.06	4339 (1710)	.005**	3481 (1107)	3705.3 (1352)	.41	3490 (1140)	.98
Duration of Exposure (Quarters)	20.8 (9.1)	20.1 (9.0)	.67	20.5 (9.4)	.90	21.4 (8.9)	18.6 (8.2)	.20	15.0 (6.6)	.06
Peak levels > 0.3 mg/L (number)	3.3 (2.4)	4.2 (2.8)	.06	5.6 (3.1)	.0004***	3.2 (2.4)	3.9 (2.7)	.21	5.3 (3.4)	.02*
Peak levels > 0.6 mg/L (number)	0.7 (1.0)	1.1 (1.4)	.04*	1.1 (1.3)	.12	0.8 (0.9)	0.9 (0.8)	.23	1.3 (1.2)	.28
Peak level (highest level in entire history, ug/L)	610 (290)	854 (640)	.0003***	844 (658)	.006**	600 (289)	885 (626)	.0006***	677 (254)	.47
Average urine mercury, 1955-56 (ug/L)	263 (128)	303 (145)	.10	333 (138)	.15	256 (120)	309 (123)	.08	306 (126)	.29

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$
a. Student t test.

electrodiagnostic evidence of polyneuropathy, although only 7 subjects were in the group. For this group, the duration of exposure was higher in the subjects without evidence of polyneuropathy, approaching statistical significance (p=0.06).

G. Description of Polyneuropathy in Exposed Subjects Having Abnormal Evaluations.

To determine the magnitude or severity of impairment in the 18 mercury exposed restricted subjects with clinical polyneuropathy and the 7 mercury exposed restricted subjects with clinical and electrodiagnostic evidence of polyneuropathy, results of their neurologic and electrodiagnostic examinations were compared to results from restricted control subjects (Tables 5-12 and 5-13). In patients with clinical polyneuropathy, neurologic abnormalities were most apparent in the lower extremities, although tremor also was abnormal compared to unexposed control subjects. The most statistically significant differences involved joint position, touch-pressure, and vibratory sensation, all large fiber or posterior column modalities. Muscle stretch reflexes were significantly reduced as well, consistent with peripheral nervous system involvement. The majority of these findings were complicated by the existence of significant interaction with the baseline variables. The most clinically significant differences (clinically recognizable differences that would be apparent in an individual subject) involved measures of distal vibratory sensation and hypoactive achilles reflexes. Comparison of these exposed subjects with polyneuropathy to 17 unselected control subjects with diabetes mellitus demonstrated only one significant difference, namely increased sustension

TABLE 5-12

Results of the Clinical and Quantitative Neurologic Examination. Comparison of Mercury Exposed Subjects from the Restricted Group with Clinical Evidence of Polyneuropathy and Clinical and Electrodiagnostic Evidence of Polyneuropathy to Restricted Unexposed Subjects. Adjusted Means and (S.E.)

Response/Measure	Unexposed (n=201)	Mercury Exposed, Clinical Polyneuropathy (n=18)	p-value[a]	Unexposed (n=201)	Mercury Exposed, Clinical & EMG Polyneuropathy (n=7)	p-value[a]
STRENGTH:						
Proximal strength (%)[c]	0.00	0.02	.18	0.00	0.05	.08
Distal strength (%)	0.31	0.70	.73	0.4	1.4	.19
Grip strength (Kg)[d]	43.9(.54)	43.0(1.9)	.48	44.1(.54)	40.2(3.0)	.15
TREMOR:						
Coordination-arms (%)	12.1	8.1	.27	11.1	11.8	.55
Coordination-legs (%)	2.4	9.8	.04*	2.4	15.8	.04*
Sustention tremor (%)	25.7	51.7	.01*	25.6	34.6	.31
Acc Tremor RMS (mm/s*2)	.81(.03)	1.14(.09)	.0004b***	.80(.02)	1.0(.13)	.08
Acc Tremor Ave Amp	.63(.02)	.92(.07)	.0002b***	.62(.02)	.82(.10)	.07
SENSATION:						
Joint position (#/10)						
Hand	.02(.01)	.07(.04)	.16	.02(.01)	.08(.05)	.24
Foot	.09(.05)	1.2(.18)	<.0001b****	.08(.03)	1.3(.18)	<.0001b****
Pin-pain, distal/proximal (%)						
Hand	176.2(7.9)	205.6(27.6)	.28	176.6(7.9)	229.9(44.7)	.21
Foot	126.9(5.9)	125.8(20.3)	.91	127.2(5.9)	127.6(33.1)	.97
Two-point discrimination (mm)						
Hand	4.4(.11)	4.7(.37)	.41	4.4(.11)	5.1(.59)	.24
Foot	32.1(.8)	40.9(2.6)	.001b**	32.0(.8)	44.5(4.3)	.003b**
Touch-pressure (log mg)						
Hand	3.5(.03)	3.6(.1)	.39	3.5(.03)	3.7(.16)	.26
Foot	3.8(.03)	4.4(.1)	<.0001b****	3.8(.03)	4.7(.18)	<.0001b****
Vibration (seconds)						
Hand	8.1(.21)	8.6(.75)	.46	8.1(.21)	8.4(1.2)	.72
Foot	15.3(.32)	21.2(1.2)	<.0001b****	15.2(.31)	22.7(1.9)	<.0001b****
REFLEXES:						
Muscle Stretch reflexes:						
Biceps	2.03(.06)	1.53(.20)	.008b***	2.03(.06)	1.35(.31)	.03*
Brachioradialis	1.92(.06)	1.53(.20)	.02b*	1.92(.06)	1.50(.32)	.12
Quadriceps	2.31(.06)	1.91(.19)	.03b*	2.31(.05)	1.59(.31)	.02*
Achilles	1.68(.06)	0.75(.21)	.0001****	1.69(.06)	0.97(.34)	.006b**

* p < .05, ** p < .01, *** p < .001, **** p < .0001

a. Covariance analysis used for parametric data: test for difference in adjusted means, adjusting for age (years) and lead exposure (no, yes). Fisher Exact test of cell frequencies used for categorical (%) outcome measures.

b. Significant interaction for differences in coefficients of adjustors.

c. Positive indicates presence of abnormal conditions for all percentile scores except pin-pain (parametric measure).

TABLE 5-13

Results of the Electrodiagnostic Evaluation. Comparison of Mercury Exposed Restricted Subjects with Evidence of Polyneuropathy and Clinical and Electrodiagnostic Evidence of Polyneuropathy to Restricted Unexposed Subjects. Adjusted Means and (S.E.)

Response	Unexposed (n=150)	Mercury Exposed, Clinical Polyneuropathy (n=15)	p-value[a]	Unexposed (n=150)	Mercury Exposed Clinical & EMG Polyneuropathy (n=4)	p-value[a]
Sensory Amplitude (uV)						
Sural	8.8(.3)	7.2(1.1)	.36	8.9(.3)	5.8(1.6)	.21
Median	17.8(.5)	16.7(1.8)	.56	17.9(.5)	11.8(2.5)	.02*
Ulnar	14.7(.5)	15.0(1.5)	.83	14.8(.4)	10.5(2.2)	.06
Sensory Nerve Conduction Velocity (m/s)						
Median	55.4(.4)	53.9(1.3)	.26	55.5(.4)	53.0(2.0)	.23
Ulnar	57.8(.4)	58.4(1.3)	.69	57.9(.4)	55.2(2.0)	.19
Sensory Distal latency (ms)						
Sural	3.7(.03)	3.7(.1)	.99	3.7(.03)	4.0(.2)	.07
Median	3.4(.03)	3.6(.1)	.16	3.4(.03)	3.9(.2)	.003b**
Ulnar	3.4(.02)	3.4(.08)	.56	3.4(.02)	3.7(.1)	.02*
# Sensory Nerve Abnormalities	1.98(.15)	3.2(.51)	.03*	1.93(.14)	5.68(.7)	<.0001b****
Motor Amplitude (mV)						
Ulnar	10.4(.16)	10.5(.55)	.87	10.4(.16)	9.7(.8)	.43
Tibial	8.2(.28)	9.0(.99)	.48	8.3(.27)	6.7(1.5)	.28
Motor Conduction Velocity (m/s)						
Ulnar	57.9(.35)	56.6(1.2)	.32	57.9(.4)	54.4(1.7)	.06
Tibial	44.2(.33)	42.1(1.2)	.09	44.3(.34)	40.4(1.8)	.03*
Motor Distal Latency (ms)						
Ulnar	2.8(.03)	2.8(.09)	.66	2.8(.03)	3.0(.14)	.06
Tibial	4.4(.05)	4.5(.17)	.83	4.4(.05)	4.5(.25)	.97
# Motor Nerve Abnormalities	.41(.06)	.87(.22)	.05*	.40(.06)	1.6(.3)	.0005***
SENSORY						
Amp % of Normal Mean[c]	49.9(1.2)	46.9(4.2)	.49	50.4(1.2)	34.4(5.9)	.009**
CV % of Normal Mean	94.0(.6)	92.9(1.9)	.58	94.1(.6)	89.2(2.8)	.09
TMCV % of Normal Mean	92.2(.6)	90.3(2.1)	.39	92.4(.6)	83.6(2.9)	.004**
MOTOR						
Amp % of Normal Mean	77.5(1.4)	80.8(4.8)	.52	77.9(1.4)	68.1(6.9)	.17b
CV % of Normal Mean	95.4(.5)	92.4(1.8)	.13	95.5(.5)	88.6(2.6)	.01b*
TMCV % of Normal Mean	98.9(.7)	97.0(2.6)	.48	99.0(.7)	92.6(3.6)	.09

* p < .05, ** p < .01, *** p < .001, **** p < .0001

Amp = Amplitude; CV = Conduction velocity; TMCV = Terminal Conduction Velocity.

a. Covariance analysis: test for difference in adjusted means, adjusting for age (years), height (inches), weight (pounds), finger volume (cm sq.), and lead exposure (no, yes).

b. Significant interaction for differences in coefficients of adjustors.

c. Percent of young adult normal mean, not adjusted for age.

tremor in exposed subjects, indicating that the magnitude of peripheral involvement was comparable to that found in association with diabetic polyneuropathy.

Comparison of the electrodiagnostic evaluations for the 18 mercury exposed, restricted subjects with clinical polyneuropathy to evaluations from 150 restricted control subjects demonstrated only two significant differences (Table 5-13), although performance was superior for all measures in control subjects. The two significant differences were the total number of sensory and motor nerve abnormalities (both higher in the clinical polyneuropathy compared to the control group). The latter finding demonstrated substantial interaction with the baseline variables. As would be expected, mercury exposed subjects with both clinical and electrodiagnostic evidence of polyneuropathy had many significant electrodiagnostic differences when compared to control subjects. (Differences existed by definition in selection of this group). The electrodiagnostic summary variables demonstrated the largest differences, particularly those involving sensory evaluations (total number of sensory nerve abnormalities, sensory amplitude and terminal conduction velocity as percentage of the normal mean), although motor conduction velocity and motor terminal conduction velocity as percentage of the normal mean also were significantly reduced. Again, many of the differences demonstrated significant interaction with baseline variables. The nature of the electrodiagnostic abnormalities (predominant decrease in sensory amplitude, mild decrease in motor amplitude, slight decrease in conduction velocity and terminal conduction velocity) was characteristic of a mild sensorimotor (sensory greater than motor) axonal polyneuropathy without evidence of primary demyelination.

H. Comparison of Subjects with Abnormal Sustension Tremor to Subjects with Polyneuropathy.

Although both abnormal tremor and polyneuropathy have been associated with elemental mercury exposure, it never has been established that the same subjects demonstrate both findings. The clinical significance of these observations as they relate to a potential toxic etiology would be logically enhanced if both abnormalities were not independent. To evaluate this further, the clinical summary variables for tremor and polyneuropathy were examined.

The clinical classification of sustension tremor (yes, equivocal, no) was compared to the clinical classification of polyneuropathy (yes, equivocal, no) using a chi-square analysis. The hypothesis that the two measures were independent was rejected for the total group ($X2=17.6$; $p=0.001$). Similar findings were demonstrated when the analysis was repeated for the restricted group and using only two categories (definitive abnormality vs. equivocal or no abnormality). In the latter, 25 of the 44 subjects identified as having polyneuropathy also had abnormal sustension tremor (57%). Of the 349 remaining subjects, 96 (28%) had abnormal tremor ($X2= 15.7$; $p < 0.001$) Comparison using only the 32 subjects with clinical evidence of polyneuropathy who also had electrodiagnostic confirmation did not demonstrate a statistically significant relationship to tremor.

I. Evaluation of Excluded Subjects.

The purpose of developing a restricted subject group was to exclude subjects with known or suspected abnormalities unrelated to mercury exposure that could influence tests results. Because few significant neurologic or electrodiagnostic differences existed between mercury exposed or control subjects in either the total group or the restricted group, it was unlikely that mercury exposure could be associated with some previously unrecognized association (e.g. malignancy, diabetes mellitus, etc.). The group of 108 excluded subjects was distributed evenly between the mercury exposed (54) and control subjects (54). Subdivision of the excluded subjects into categories based upon presumed etiology is shown in Table 5-14, expressed as a percentage of either the mercury exposed or control

TABLE 5-14

Grouping of Disorders Identified from Clinical Examination
Comparison of the Percentage of Subjects Excluded from
the Mercury Exposed and Control Groups

Category of Etiology	Mercury Exposed Percent-Positve (n=247)	Control Percent-Positive (n=255)	P-value[a]
Neoplasm with or without chemotherapy or radiation therapy	2.1	1.2	.36
Trauma	0.8	1.6	.35
Toxic or medication exposure	2.9	1.6	.27
Structural	3.3	2.9	.49
Vascular	1.2	2.5	.26
Psychiatric	0.8	0.4	.50
Inflammatory	0.8	0.4	.50
Connective tissue disorder	0.8	0.4	.50
Metabolic	9.5	6.6	.15
Nutritional	0.4	0.8	.50
Unknown	7.4	3.3	.03*

* $p < 0.05$

a. Fisher exact test of cell frequencies.

groups. None of the categories involving known etiology demonstrated significant differences in distribution between exposed and control groups. The only category with a significantly uneven distribution was the subdivision designated "unknown etiology", demonstrating a greater percentage of subjects with neurologic abnormality in the mercury exposed group.

Comparison of clinical and electrodiagnostic results for mercury exposed and control subjects in the unknown etiology group demonstrated only one significant difference. Namely, sensory amplitude expressed as a percentage of the normal mean was significantly lower in the control than the mercury exposed group. Similar comparison of the mercury exposed subjects in the unknown etiology group to the restricted control subject group demonstrated several significant differences. All of the differences in sensation represented poorer performance in the mercury exposed group. Measures that were significantly different included two-point discrimination in the hand, vibration sensation (hand and foot), and joint position sensation (foot). All of the muscle stretch reflexes were increased in the mercury exposed compared to the control group. None of the electrodiagnostic measures was significantly different. Based upon the clinical and electrodiagnostic findings, it appeared that the abnormalities in the unknown etiology group could not be explained by a peripheral nervous system disorder but would better reflect central nervous system dysfunction based upon the increased muscle stretch reflexes.

The clinical data sheets for the 18 mercury exposed subjects having neurologic abnormalities of unknown etiology (but felt to be inconsistent with previously described elemental mercury associated abnormalities) were reviewed. The predominant abnormalities were consistent with myelopathy

(undefined level) in 11 subjects. The large proportion of mercury exposed subjects having clinical evidence of nonspecific myelopathy was consistent with the findings on the individual components of the quantitative neurologic examination and the electrodiagnostic evaluations. Six other subjects had abnormal tremor plus additional findings suggestive of Parkinsonism or a family history of similar tremor. The remaining subject had evidence of dementia.

Review of the clinical data sheets for the 7 control subjects having neurologic abnormalities of unknown etiology revealed 4 subjects with findings suggestive of myelopathy, 2 subjects with abnormal tremor plus evidence of parkinsonism or a family history of tremor, and 1 subject with idiopathic postural hypotension. Although the proportion of subjects with findings suggestive of myelopathy was higher in mercury exposed than control subjects (11 of 236 vs. 4 of 251), the difference was marginally statistically significant (4.4 versus 1.6%; $X2=3.59$, $p=.06$. However, it was an unexpected finding, and is based on a small number of subjects. Comparison of urine mercury history variables for the 11 exposed subjects with myelopathy to exposed subjects with a normal clinical examination demonstrated no significant differences between groups.

DISCUSSION

A. Inter-examiner Reproducibility.

The results of the crossover comparison of the two neurologists indicated good inter-examiner reproducibility for the two clinical neurologists. The minor differences identified were felt to be of limited clinical significance. Because none of the thirty-eight subjects examined had more than mild abnormalities on examination and because only six of the

subjects had underlying medical conditions that excluded them from the final analyses (all had mild diabetes mellitus), failure to demonstrate a significant correlation between examiners for measures of lower extremity coordination and joint position sensation of the index finger reflected small scoring differences on a very small number of subjects. For example, only one subject had more than one error per ten trials on the joint position measurement. The comparison therefore had limited meaning in this setting, and the test is of established clinical significance as part of the conventional neurologic examination. That three of the four tests involving assessment of muscle stretch reflexes demonstrated significant mean differences between examiners is consistent with a previous study (Kuzma et al., 1964) that found significant differences between neurologists using the same grading system to estimate reflexes. Although the means differed, the difference was less than one-half grade, and the measures demonstrated a significant correlation with relatively high correlation coefficients for biological measures ($0.34 < r < 0.86$). This indicates that the examiners differed by a fixed amount but were able to discriminate relative increases or decreases in reflexes. The remaining tests with significantly different means included measures of two-point discrimination (index finger) and pin-pain sensation (first toe). Like the reflex measurements, both tests demonstrated significant correlation between examiners, with correlation coefficients of $r = 0.49$ and 0.33 respectively. The statistically significant different means for two-point discrimination may not be clinically important since the observed mean difference was only 1.2 mm. It is possible that two-point discrimination measurements on 0.5 mm intervals may be too fine (Kuzma et al, 1964). That the minor inter-physician differences were of limited clinical significance

is reflected by the extremely good agreement for the summary variables. Twenty-six of 38 subjects were classified identically by both physicians. Fourteen were classified as having a normal examination, 4 as having a mild (equivocal) polyneuropathy, and 8 as having a definite polyneuropathy. Of the remaining twelve subjects, all of the differences were between mild equivocal and definite polyneuropathy (seven) or normal examination versus mild equivocal polyneuropathy (five). No subjects were classified as having a normal examination by one neurologist and a definite polyneuropathy by the other.

B. Simple Comparisons Based Upon Mercury Exposure Status

The simple comparisons of the clinical and quantitative neurologic examination results demonstrated few significant differences between the mercury exposed and control groups, and the slightly increased tremor (quantitative measures) in mercury exposed subjects in the total group comparison was not present in the restricted group evaluation. Nevertheless, the finding of increased tremor in mercury exposed compared to control subjects was similar to previous results. The only other measures approaching statistical significance included strength (distal and grip), touch-pressure sensation (hand), and the percentage of subjects with a positive snout reflex. All differences favored better performance (less abnormality) in the control group. None of the above differences persisted in the restricted group analysis, although significantly more errors were made in joint position testing (foot) in mercury exposed than control subjects. This measure demonstrated significant interaction between baseline variables and only a small number of subjects demon-strated abnormality. Because clinical evidence of joint position sensation impairment is apparent only in moderately-severe polyneuropathy or

abnormal, this isolated finding has no apparent clinical meaning. Overall, no clinically significant differences were demonstrated, either before or after exclusion of subjects with evidence of underlying abnormalities that could influence the neurologic examination but were not attributable to mercury exposure.

Similarly, simple comparison of the results of the electrodiagnostic evaluation demonstrated only one significant difference; a relatively reduced median sensory amplitude in the mercury exposed compared to the control group. Summary measures, expressed as a percentage of the young adult normal measures, demonstrated relatively low sensory and motor amplitudes overall, compared to the slightly reduced conduction velocities (both distal extremity, e.g., elbow to wrist, and terminal portion of nerve). These findings are consistent with the distribution of age in the subject group and not unexpected.

C. Regression Analysis.

Regression analysis showed a significant relationship between peak and cumulative urine mercury measures and several of the clinical and quantitative neurologic measurements including strength (proximal and distal), tremor (sustension and quantitative) and sensation in the lower extremity (joint position, two-point discrimination, touch-pressure, and vibratory sensation). However, it was shown that several of these significant regression trends were dependent upon the results of a very small number of individuals (no more than 3) who were the most extreme outliers with respect to clinically apparent abnormalities. The two urine mercury history measures used in the regression analysis were chosen because of our previous experience that these measures best reflected mercury exposure.

All significant correlation coefficients between neurologic findings and urine mercury history variables were small (r=0.10 to 0.16) and much smaller than we have reported previously (r=0.19 to 0.39) for subjects with low level but ongoing mercury exposure (Albers, 1982).

Regression analysis of the electrodiagnostic evaluation demonstrated only a few significant relationships between peak measures of urine mercury and electrodiagnostic abnormalities. Similar to the comparison with neurologic findings, all of the significant correlation coefficients between electrodiagnostic findings and urine mercury history variables were small (r=0.10 to 0.11) and substantially smaller than those we have reported previously. In a prior study with moderate-level, ongoing exposure, correlation coefficients as high as r=0.72 and 0.61 were demonstrated for average urine mercury levels and sensory and motor distal latencies, respectively. In a subsequent study involving a larger number of subjects but lower ongoing exposure levels, correlation coefficients of r=0.19 to 0.39 were demonstrated, with sensory terminal conduction velocity demonstrating the highest (negative) values. We had previously believed that the correlation coefficients tended to increase with increasing exposure. Our current findings would suggest both the magnitude of exposure and the interval between exposure and evaluation are important; with prolonged intervals, correlation coefficients, while still significant, decrease in magnitude.

The finding that the number of abnormal motor nerve measurements correlated significantly with the peak urine mercury measure was surprising in that the number of sensory nerve abnormalities did not demonstrate statistically significant similar trends. There is a suggestion of a possible threshold effect for individuals with a history of more than one

urinary mercury level above 0.6 mg/L and either the number of sensory or motor nerve abnormalities on the electrodiagnostic tests. The relationship appears somewhat stronger for the motor nerve abnormalities than for the sensory abnormalities. This relationship was not dependent on a few individuals

One of the significant covariates in some of the multiple regression analyses was the presence or absence of prior lead exposure (questionnaire) but it was not a significant covariate for the number of abnormal motor nerve measurements. Like mercury, lead demonstrates nervous system toxicity in both organic and inorganic forms. The effects are known to be age dependent and, in adults, are associated with polyneuropathy. In context of the present study, lead associated polyneuropathy is of interest because of its prominent motor nerve predilection, there being minimal or no sensory symptoms or signs. The classic descriptions of lead neuropathy include evidence of upper extremity involvement, often in a radial nerve or C8–T1 nerve root distribution. Such a distribution is uncharacteristic of most toxic neuropathies (Dapsone neuropathy would be an exception). The question of lead exposure is further evaluated in Chapter 9.

Taken together, the results of the clinical and electrodiagnostic evaluations suggest only a few statistically significant mercury related associations including abnormal sustension tremor, decreased strength (proximal and distal) distal lower extremity sensory abnormalities, and an increased number of motor nerve electrodiagnostic abnormalities. Most of the relationships could be explained by a few abnormal subjects and all of the abnormalities were relatively mild. The combined sensory and electrodiagnostic abnormalities were insufficient to conclude that prior mercury exposure was associated with a chronic sensorimotor peripheral

polyneuropathy. The absence of a significant relationship between urine mercury history variables and muscle stretch reflexes, particularly the achilles reflex, or abnormal sensory responses in the electrodiagnostic evaluation, argues against the presence of a persistent sensory polyneuropathy of substantial magnitude. The dose-response studies did suggest a significant relationship between prior mercury exposure and declining neurologic performance, but the combined abnormalities were insufficient to determine whether they were associated with peripheral or central nervous system dysfunction, or even a combination of both. Combined upper and lower motor neuron findings, for example, would make averaged muscle stretch reflexes over subjects uninterpretable. Furthermore, if there was a threshold level effect that had to be exceeded prior to developing impairment, or if previous mercury associated abnormalities resolved over time, the above comparisons would be diluted by mercury exposed subjects who no longer demonstrated abnormality. For these reasons, comparison of subjects with high mercury exposure to those with low exposure and comparison of urine mercury history variables for subjects with specific neurologic findings to subjects with normal neurologic examinations, after correction for age and other significant covariates, was performed.

D. Selective Evaluation of Subjects with High Mercury Exposure.

Comparison of subjects with one or more urine mercury peaks above 0.6 mg/L, a conventional measure of substantial exposure, to subjects without such peaks demonstrated significant differences in several neurologic performance measures. All differences reflected poorer performance in the higher compared to the lower exposure group. In general, the same variables identified in the regression analysis demonstrated significant differences in the stratified group comparison. In summary, the group of

exposed subjects with one or more urine mercury determinations above 0.6 mg/L had slightly poorer performance on several measures of sensory or motor function, including quantitative tremor. Although the simple comparisons described above did not identify the relationship as firmly, stratification into high and low level exposure groups suggested an association between impaired performance and mercury exposure.

It is not possible to identify one central or peripheral nervous system disorder which could explain all the differences between the two groups. For example, the identified sensory differences could be on the basis of either a central or peripheral nervous system impairment, as could the finding of increased tremor in the higher mercury exposure group. On the other hand, the increased prevalence of Babinski and snout responses in the higher compared to lower mercury exposure group cannot be attributed to a peripheral lesion. This increased prevalence of Babinski and snout reflexes in a higher exposed group should be interpreted cautiously because it has not been associated in the past with this level of mercury exposure in other studies. In addition, the high prevalence of snout reflex in the low exposure group confirms that this reflex may be predominantly a normal aging phenomenon. Clinically the snout reflex is associated with bilateral supranuclear (upper motor neuron) lesions or diffuse cerebral degeneration. The Babinski response is associated with upper motor neuron dysfunction at any level of the corticospinal pathway. We have no additional evidence to suggest that mercury exposure in these workers is causing diffuse cerebral degeneration. Nevertheless, subjects in the mercury exposed group were significantly less likely to have a normal examination; the abnormalities could not be explained by the presence or absence of polyneuropathy alone.

By further dividing the exposed subjects into groups based upon urine mercury peaks, we were able to demonstrate that the greatest percentage of subjects with clinical evidence of polyneuropathy were in the highest exposure group. The relative risk of demonstrating evidence of polyneuropathy was increased approximately two to three fold compared to the lower exposure groups, after adjusting for potential confounding factors. It is probable that about five exposed workers have a residual mild polyneuropathy related to mercury exposure, based upon this analysis.

Similar comparison of the electrodiagnostic evaluations of higher to lower level of exposure subjects demonstrated only one significant difference between groups (median sensory distal latency), and a slightly greater number of significant sensory and motor nerve abnormalities in subjects with two or more urine mercury peaks above 0.6 mg/L. These findings cannot be explained on the basis of a central nervous system abnormality but are characteristic of a peripheral sensorimotor axonal polyneuropathy, consistent with prior studies that have established the association between elemental mercury exposure and polyneuropathy.

The observation that the relationship between a history of substantial mercury exposure and specific abnormality is stronger for electrodiagnostic motor nerve compared to sensory nerve abnormalities is surprising because our prior studies demonstrated that sensory abnormalities were more strongly related to mercury exposure. Lead is accepted as a cause of motor nerve neuropathy. Our regression equations contained a term for lead exposure, but lead was not found to be a significant predictor for either motor or sensory abnormalities on electrodiagnostic evaluation.

E. Age and Exposure Interaction.

The observation for some measures that aging may unmask prior subclinical damage is important. The findings that some motor and sensory measures demonstrating significant differences between exposed and unexposed subjects were age-dependent is consistent with existing models of remote environmental neuronal damage that becomes unmasked as a consequence of age-related neuronal attrition. Such models have been used hypothetically to explain presumed degenerative neurologic disorders such as pre-senile dementia, parkinsonism, and motor neuron disease. Diseases that provide substantiation of this hypothesis include late progression of prior poliomyelitis, ALS-dementia complex of Guam, trauma related to boxing with subsequent encephalopathy and parkinsonism, and remote radiation associated plexopathy or myelopathy. The model is dependent upon a threshold effect, whereby neuronal loss below a certain level results in neurologic impairment. Subthreshold damage initially results in no identifiable impairment. However, over time, the natural age-related neuronal attrition (a well-identified phenomenon) results in subsequent development of neurologic findings. The severity of the initial damage would directly influence the latent interval between exposure and appearance of neurologic impairment in such a model. Presumably, different areas of the nervous system demonstrate different susceptibility to specific neurotoxins. Such a model has obvious therapeutic and etiologic implications.

F. Urine Mercury Comparisons for Abnormal and Normal Exposed Subjects.

The stratified exposure comparisons and the urine mercury history variable comparisons for subjects with and without clinically abnormal tremor suggested a weak association between abnormal tremor and increasing

mercury exposure. However, the only statistically significant relationship was an increased urine mercury peak level in subjects with abnormal tremor in the total group comparison. This urine mercury history variable is the same one that demonstrated the most significant findings in the comparison of subjects with and without polyneuropathy, and suggests that the magnitude of exposure, rather than the duration of exposure, may be associated with neurologic abnormality.

The tremor results were similar to those of earlier studies involving chlor-alkali workers. There, we found that urine mercury peaks in excess of 0.5 mg/L were most important in predicting increased tremor. Our current results support this observation and suggest that the abnormality is long-lasting following remote exposure, a surprising finding because we have previously demonstrated that tremor tended to decrease after subjects were removed from ongoing mercury exposure.

Subjects with clinical or clinical and electrodiagnostic evidence of polyneuropathy had significantly higher mercury exposure as demonstrated by the urine mercury history variables then did subjects with normal examinations. The most consistent significant results were for the urine mercury peak levels or number of peak levels exceeding 0.3 mg/L. The explanation for the association between the magnitude of the highest urine mercury peak and polyneuropathy found in Table 5-11 is the higher percentage of individuals with polyneuropathy in those subjects having peak urine mercury levels above 0.85 mg/L (Table 5-8A). The duration of exposure measure demonstrated little relationship to the presence or absence of polyneuropathy, and approached significance in the restricted group suggesting longer exposure in subjects without polyneuropathy. Although subjects with polyneuropathy tended to be older than subjects

without polyneuropathy, the urine mercury history variables did not demonstrate a similar age dependence. These findings suggest that higher levels of mercury exposures are associated with more evidence of polyneuropathy long after exposure than chronic, low-level exposures. These data cannot determine whether subjects with chronic, low-level exposure previously had polyneuropathy that had resolved by the time of the current evaluation.

G. Description of Polyneuropathy in Exposed Subjects having Abnormal Examination.

In the present subject group, it is not surprising that remote mercury exposure that ceased twenty or more years before evaluation did not have a dramatic or even clearly demonstrable peripheral effect. It might have been anticipated, however, that sensory abnormalities related to a polyneuropathy or neuronopathy would be more readily detectable than motor abnormalities because of the extensive axonal sprouting of motor nerves that follows partial denervation and the clinical observation of persistent sensory deficit long after motor impairment has resolved in patients with reversible polyneuropathy. The clinical examination/dose-response relationships partially supported this idea, in that deteriorating sensory function was related significantly to increasing peak urine mercury measures, most apparent in the distal lower extremity. This relationship has clinical validity, in that the longer, most distal sensory fibers are those most likely to demonstrate persistent abnormalities. The absence of a relationship between mercury exposure measures and reduced muscle stretch reflexes can be interpreted to reflect return of reflexes, as is commonly seen in resolving polyneuropathy, absence of peripheral nervous system involvement, or a combination of both. Average urine mercury levels were

higher in the present study (0.26 mg/L during the years of highest exposure; 1955 and 1956) than in our previous two studies (0.09 mg/L and 0.15 mg/L, respectively), although exposure in both of those studies was ongoing, rather than remote. Little is known about recovery from polyneuropathy caused by an exogenous toxin. However, using experience with other forms of reversible polyneuropathy, recovery of muscle stretch reflexes is common.

Evaluation results from control subjects with diabetes mellitus were compared to those from mercury exposed subjects with polyneuropathy to demonstrate the relative magnitude of the findings. Exposed subjects had significantly increased sustension tremor compared to the diabetic control group but no other neurologic or electrodiagnostic differences. The majority of diabetic subjects (23 of 42) had clinical evidence of polyneuropathy, a very common, clinically and statistically significant consequence of the disease. That no differences other than increased sustension tremor existed between mercury exposed subjects with polyneuropathy and unselected diabetic control subjects, suggests that the mercury associated polyneuropathy is of a magnitude comparable to that seen in mild diabetic polyneuropathy, and therefore, not clinically insignificant.

It is possible that some of the sensory abnormalities were on a central rather than a peripheral basis. Findings suggestive of central nervous system involvement include the association between increased tremor and mercury exposure, the significantly increased percentage of subjects with high mercury exposure having Babinski and snout reflexes, and the findings suggestive of unexplained myelopathy in a greater proportion of exposed than non-exposed subjects.There have been reports of fasciculations

in patients with mercury oxide exposure having clinical findings said to resemble those found in organic mercury intoxication and ALS. Although the peripheral abnormalities have been felt to mimic ALS, we had not previously identified subjects with clinical electrodiagnostic evidence of pure motor involvement.

H. Comparison of Subjects with Abnormal Sustension Tremor to Subjects with Polyneuropathy.

The consistent relationships between abnormal tremor, polyneuropathy, and increased elemental mercury exposure measures in this and prior studies provides ongoing consensual validity that the association exists. However, it has not been known whether the same subjects demonstrating abnormal tremor also have evidence of polyneuropathy. Results of the current evaluation have established a statistically significant relationship between the clinical classifications of tremor and polyneuropathy for both the total and restricted groups. However, classification of polyneuropathy, using the more strict definition of both clinical and electrodiagnostic measures, did not demonstrate a significant relationship with the tremor classification. These results suggested that, while many exposed subjects had both abnormal tremor and polyneuropathy, there were many subjects that had one or the other, but not both. That the subjects having abnormal tremor were not necessarily the same ones having evidence of abnormal sensation argues against the possibility that the sustension tremor was actually a sensory tremor, similar to that seen in chronic inflammatory demyelinating polyneuropathy, rather than a manifestation of central nervous system abnormality.

I. Evaluation of Excluded Subjects.

That there was an equal number of excluded subjects from the exposed and control groups suggested that a previously unidentified neurologic abnormality associated with mercury exposure was not being overlooked. Nevertheless, there was a significantly uneven distribution of subjects having non-specific neurologic findings of "unknown etiology" among exposed subjects. Within the group, the most common abnormalities were consistent with nonspecific myelopathy. This finding was of marginal ($p=.06$) significance and of unknown clinical significance. Nevertheless, the association between environmental mercury exposure and findings of non-specific myelopathy may reflect subtle central nervous system abnormalities consistent with neuronal attrition.

The association of myelopathy and mercury exposure was not supported by comparing these subjects' urine mercury history variables to exposed subjects with normal examinations, in that there were no significant differences between the two groups.

SUMMARY

We examined 502 subjects, 247 of whom had occupational elemental mercury exposures 20-35 years previously, to identify potential exposure-related neurologic abnormalities. Few significant ($p < 0.05$) differences existed between exposed and unexposed subjects. However, multiple linear regression analysis demonstrated several significant correlations between declining neurologic function and increasing exposure using urine mercury determinations from the exposure interval. Subjects with urine mercury peak levels above 0.6 mg/L demonstrated significantly poorer performance than remaining subjects, including decreased strength, decreased

coordination, increased tremor, decreased sensation, and increased prevalence of Babinski and snout reflexex, consistent with central and peripheral nervous system involvement. Furthermore, subjects with clinical polyneuropathy had significantly higher peak levels than normal subjects (0.85 vs. 0.61 mg/L; p=0.0003), but not increased exposure duration (20.1 vs. 20.8 quarters; p=0.67), and 28% of subjects with peak levels above 0.85 mg/L had clinical evidence of polyneuropathy, compared to 10% of remaining subjects (p=0.005). Although exposure was not age-dependent, several neurologic measures showed significant age-mercury interaction suggesting that natural neuronal attrition may unmask prior subclinical abnormalities.

6. RESULTS OF TREMOR AND BEHAVIORAL TESTS

Tests in this section are grouped into three subsections. The first subsection describes results of the tremor tests. The second subsection describes results of tests that measured motor skills including one-hole dexterity, simple reaction time, and eye-hand coordination. The third subsection describes results of tests that measured cognitive skills including short-term memory, visual memory, symbol-digit, and vocabulary tests.

TREMOR TEST RESULTS

Subjects included in analysis. The subject sample consisted of those classed as exposed and control. Twenty-two subjects were excluded from the initial analysis because of conditions detected in the neurological examination that could cause an abnormal tremor and therefore reduce the power of statistical tests to detect a mercury effect. The conditions we excluded were:

- Parkinson's disease
- Heavy alcohol use
- Familial tremor
- Movement disorder
- Cerebral hemorrhage
- Cerebral infarction
- Use of Theophiline medication.

Four individuals were excluded because of Parkinson's disease. No more than three individuals were excluded for each of the other conditions. None of these medical conditions were significantly related to the subjects' mercury exposure status (two-way classification, Fisher's Exact Test, $p > .20$). Altogether 12 of the 22 excluded individuals were mercury exposed. Of course, this proportion did not indicate a significant excess of exclusions within the mercury exposed group (Fisher's Exact Test $p > .5$). The twelve excluded exposed subjects' urine mercury indexes were not

significantly different from the exposed subjects whose data were included in the analysis (Mann Whitney Test).

Although the statistic is not significant, three out of four individuals with Parkinson's disease diagnosed were mercury exposed. Similarly, two out of three individuals who had a diagnosis of familial tremor were mercury exposed. Because one cannot exclude the unlikely possibility that the tremor of those with Parkinson's and familial tremor diagnoses could be at least partially associated with mercury exposure, a second analysis of tremor was performed with these individuals included.

Tremor Tests.

Tremor was measured in two different tests. First, in the medical examination, the neurologist semi-quantitatively rated each subject's tremor on a 5-point scale with categories: none, trace, mild, moderate, and severe. Second, in a separate examination, each subject's tremor was precisely quantified using the forearm tremor device.

Tremor observations from the neurological exam. The neurologist's tremor ratings showed some potentially interesting relationships with subjects' mercury exposure status. Figure 6-1 shows the distribution of tremor ratings as a function of subjects' exposure status. There were slightly more mercury exposed subjects in each tremor category above "none." Thirty one percent of the mercury exposed subjects were rated as having a trace or more tremor compared to 26 percent of the control group (Fisher's Exact Test, $p = .14$).

Some of our own and others' past work has suggested that there may be a urine mercury threshold for mercury related tremors. Therefore, in an additional analysis, subjects were divided into two groups: those who had one or more urine mercury peaks above 0.6 mg/L ($n = 105$), and those who did not have a history of such peaks ($n = 375$).

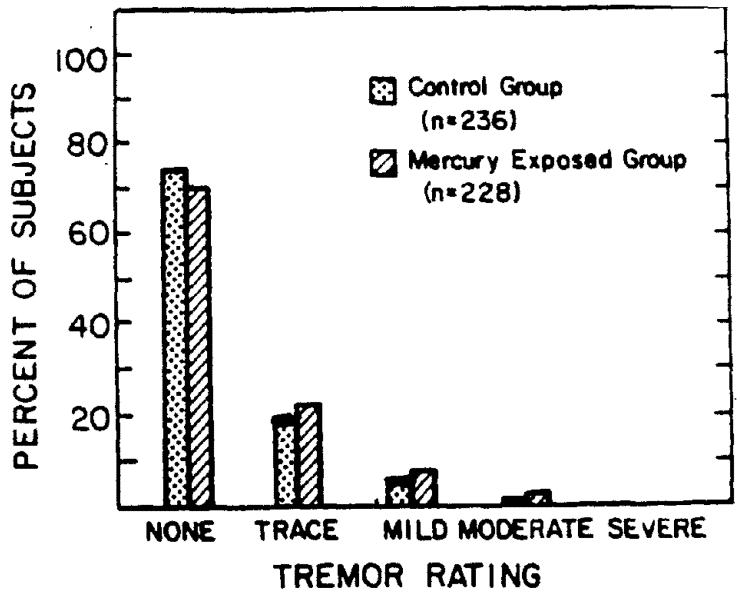


Figure 6-1. Distribution of Neurologist's Tremor Ratings within the Exposed and Control Groups.

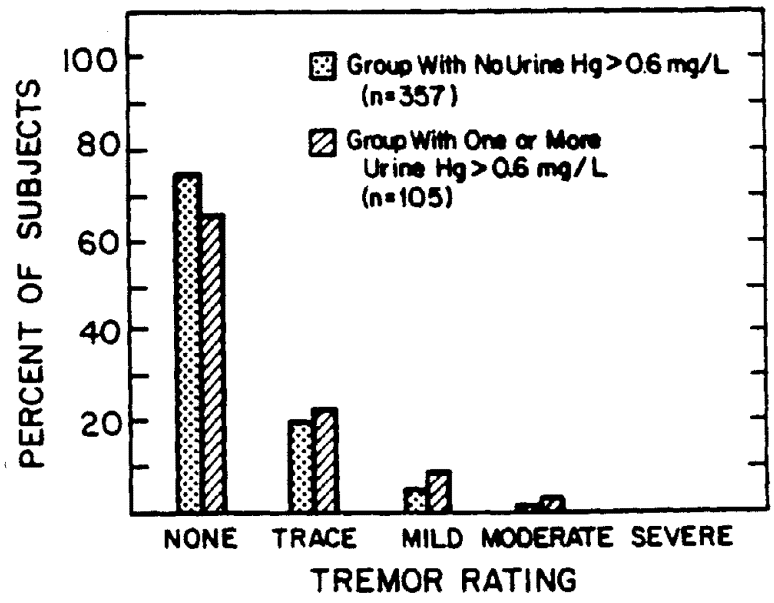


Figure 6-2. Comparison of Neurologist's Tremor Ratings for those Subjects who had Urine Mercury Peaks Over 0.6 mg/L versus Those Who Did Not Have Peaks Exceeding 0.6 mg/L.

The group with urine mercury peaks above 0.6 mg/L had a slight excess of cases in each of the tremor categories of a trace or more (Figure 6-2). Thirty four percent of the group with peaks above 0.6 mg/L had a tremor compared with only 26 percent in the other group. (Fisher's Exact Test, $p = .08$).

The proportion of subjects with a trace or more tremor apparently increased as a function of their number of historical urine mercury peaks above 0.6 mg/L. Of those who had two or more such peaks, 38 percent (17/45) were rated as having a trace or more tremor (Fisher's Exact Test, p = .10). Of those with three or more peaks above 0.6 mg/L, 59 percent (10/17) had such notable tremor. This high proportion was very significant (Fisher's Exact Test, p = .007) despite the fact that only 17 individuals had three or more peaks above 0.6 mg/L.[1] Because only three individuals had four or more peak urine levels over 0.6 mg Hg/L, the fact that two out of the three had more than baseline tremor ratings has no statistical significance. The finding that the proportion of above normal tremor ratings tends to increase with subjects' number of urine peaks above 0.6 mg/L is illustrated in Figure 6-3. None of the subjects with three or

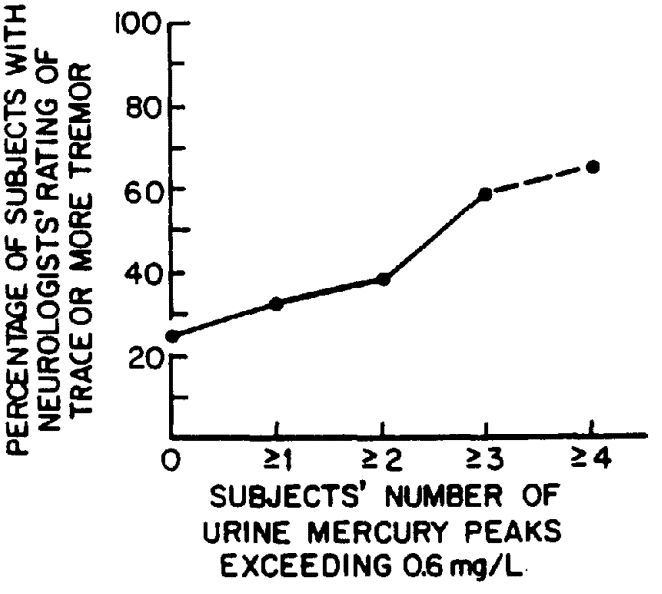


Figure 6-3. Relationship Between Subjects' History of Urine 0.6 mg/L and Proportion of Neurologists' Tremor Ratings of a Trace or More.

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[1]In computing the significance of the excess of subjects with tremor, subjects with peaks above 0.6 mg Hg/L were compared to all other subjects who included controls and exposed with no urine peaks above 0.6 mg/L. If comparisons were in reference to controls only, the latter two significance levels would be slightly improved to p = .07 and p = .006.

greater peaks had more than a mild tremor. All of the moderate tremor cases were in the none, one or two peak groups. There were no exposed subjects with a severe tremor.

Quantitative Tremor Tests

Subjects. Data from the forearm tremor measurement device were analyzed for all subjects included in the neurological tremor examination, except for 11 subjects whose data were missing. (As in the neurological tremor examination analyses, 22 subjects with potentially confounding disease conditions were excluded from this preliminary analysis.) Missed data were caused by equipment failure or inability of subjects to complete the tests. (Subjects who were wheelchair bound could not be tested. Likewise, subjects who were very frail were not asked to complete the test which required maintaining a static posture for nearly three minutes.) Six of the 11 subjects whose data were missing were formerly mercury exposed. These six had a mean integrated urine mercury index of 3.6 mg/L, exactly the same as the mean 3.6 mg/L of the exposed group as a whole. Their average peak urine mercury index was 0.55 mg/L, lower than the exposed group's mean peak level of 0.65 mg/L. Among the six exposed individuals with missing tremor data, peak urine mercury indexes ranged from 0.35 to 0.80 mg/L. This was not an unusual range compared to values that ranged up to 3.02 mg/L in the exposed group as a whole.

After eliminating subjects with missing data, the control and exposed subjects did not differ in mean age, education, height, or weight (student t, $p > .20$); nor were they different with respect to prevalence of self-reported hypertension, a possible confounder (Fisher's Exact Test, $p > .15$) (Table 6-1).

TABLE 6-1: Comparison of Exposed and Control Groups' Biographical Data for Subjects Included in Quantitative Tremor Analysis.

BIOGRAPHICAL VARIABLE	CONTROL GROUP MEAN (STD DEV) N = 229	EXPOSED GROUP MEAN (STD DEV) N = 240
Age (years)	64.2 (7.3)	64.0 (7.1)
Education (years)	11.8 (2.6)	11.8 (2.3)
Height (inches)	70.1 (2.8)	69.9 (2.8)
Weight (pounds)	184 (26)	181 (29)
Reported alcoholic drinks per week	2.6 (4.6)	2.9 (5.2)
Reported had a drinking problem in the past	4.6%	2.2%
Reported hypertension	40%	38%

Simple Comparisons of Displacement Tremor Based Exposure Status. As in our past work, the forearm tremor device was used to measure displacement tremor. (A potentiometer converted forearm displacement into a voltage which was analyzed by a computer.) Table 6-2 compares the various measures of displacement tremor as a function of two methods of categorizing mercury exposure. First the mercury exposed subjects were simply compared to controls. Second, to study a possible threshold or peak exposure effect, the group of subjects who had one or more peak urine mercury values exceeding 0.6 mg/L were compared to the group of subjects who had no peaks over 0.6 mg/L. (Note that this comparison group includes many lower exposed subjects in addition to controls.)

In Table 6-2, comparisons of the exposed group average scores to control group average scores revealed no statistically significant differences in any of the displacement tremor parameters. All tests for differences in mean tremor scores were performed using the version of Student's t test that does not require the two groups' data to have equal variance. Prior to testing, each tremor score was transformed using the transformation that caused the

data to best approximate the normal distribution shape with a skewness of approximately zero and a kurtosis of 3. The transformations used are shown in Table 6.2. As was true in our past work (Langolf et al.. 1978, 1981) there were no significant differences between measures of overall displacement tremor amplitude: RMS and average absolute levels. There was also no difference between exposed and control groups in the percentage power in the neuromuscular peak. This was the parameter most affected by mercury exposure in our past work. Likewise, there was no difference in the mean frequencies of the neuromuscular peak. Past work indicated this frequency was lower in more highly mercury exposed subjects. In the present study, a new parameter was added, a sum of the total percentage power in the 4 to 8 Hz band encompassing neuromuscular tremor activity. This was done because the summed measure may be more statistically reliable than the previous estimate of neuromuscular peak power in a single 0.2 Hz bandwidth. Comparing exposed and control group means, this new 4 to 8 Hz power measure showed the largest apparent difference (7.74% exposed versus 6.91% control) although this was not statistically significant (Student's unequal variance t, $p = >.50$).

Also in Table 6-2, comparing the higher exposure group of subjects who had one or more urine mercury peak over 0.6 mg/L to the group of those who had no such peaks, the differences in displacement tremor parameters were nearly all in directions consistent with a hypothesized residual mercury effect. The higher exposure group's mean amplitude measures are higher and the frequency is lower. Only one difference is marginally significant. The new neuromuscular 4 to 8 Hz power measure is higher in the more highly exposed group at 9.04% versus 6.84% in the remaining comparison group ($p < .10$). (The mean age and other potential confounding factors were not different between the two latter groups.)

TABLE 6-2: Comparison of Displacement Tremor Results for Two Urine Mercury Contrasts.

DISPLACEMENT TREMOR PARAMETER	TRANSFORM USED FOR SIG. TEST	CONTROL GROUP MEAN (n = 240)	EXPOSED GROUP MEAN (n = 229)	GROUP WITH NO URINE Hg >0.6 mg/L MEAN (n = 367)	GROUP WITH ONE OR MORE URINE Hg > 0.6 mg/L MEAN (n = 102)
Root Mean Square Amplitude (RMS) (mm)	Log	0.894	0.904	0.887	0.939
Average Absolute Amplitude (mm)	Log	0.657	0.667	0.652	0.699
Percentage of Total Power in Neuromuscular Peak	None	1.24%	1.23%	1.24%	1.23%
Frequency of Neuromuscular Peak (Hz)	Square	5.60	5.56	5.60	5.55
Percentage of Total Power in 4 to 8 Hz Band	Log	6.91%	7.74%	6.84%	9.04%*

*Difference marginally significant $p < .10$ (Student's t, unequal variance two-tailed test).

Acceleration Tremor Analysis. The left-hand side of Table 6-3 compares acceleration tremor parameters of the exposed and control groups. (The acceleration signal was obtained from an accelerometer mounted on the forearm tremor device. The acceleration tremor parameters were determined through on-line computer spectral analysis.) There were no statistically significant differences between the exposed and control groups' mean acceleration tremor parameters (Student's unequal variance t, $p > .10$). (Where necessary, data were transformed to approximate the normal distribution. The transformations were applied before applying the Student t test as shown in Table 6-3. The directions of the mean comparisons, however, are consistent with past observations of the effects of mercury on

TABLE 6-3: Comparison of Acceleration Tremor Results for Two Urine Mercury Contrasts.

ACCELERATION TREMOR PARAMETER	TRANSFORM USED FOR SIG. TEST	CONTROL GROUP MEAN (n = 240)	EXPOSED GROUP MEAN (n = 229)	GROUP WITH NO URINE Hg >0.6 mg/L MEAN (STD DEV) (n = 387)	GROUP WITH ONE OR MORE URINE Hg > 0.6 mg/L MEAN (STD DEV) (n = 102)
Root Mean Square Amplitude (RMS) (mm/sec^2)	Log	81.0 (31.6)	85.8 (44.7)†	80.6 (31.4)	93.0* (55.4)†
Average Absolute Amplitude (mm/sec^2)	Log	63.0 (25.1)	67.4 (38.3)†	62.7 (25.7)	73.8* (48.4)†
RMS Amplitude filtered, 4 to 8 Hz Band (mm/sec^2)	None	66.9 (28.3)	72.1 (42.1)†	66.7 (29.2)	78.9* (52.1)
Neuromuscular Peak Amplitude [Amplitude of Largest 0.2 Hz Band in 4 to 8 Hz Range, (mm/sec^2)]	Log	10.0 (1.9)	10.1 (2.4)	10.1 (2.2)	9.9 (1.9)
Frequency of Neuromuscular Peak (Hz)	None	5.0 (0.65)	4.92 (0.67)	4.97 (0.65)	4.92 (0.67)
Mean Frequency of Entire Acceleration Tremor Spectrum (Hz)	None	6.18 (0.75)	6.14 (0.73)	6.17 (0.75)	6.15 (0.71)

Significance levels:

† $p < .10$
* $p < .05$

Student's t test for means, (unequal variance version, test applied to transformed data where necessary) Levene's robust test for equality of variance.

tremor. The exposed group's amplitude measures were higher than those of the control group. The exposed group's two measures of tremor frequency were lower. On the right-hand side of Table 6-3, comparing the most highly exposed group of those workers with one or more urine mercury peaks over 0.6 mg/L to the remaining group, three measures of mean tremor amplitude were significantly higher in the more highly exposed group (Student's unequal variance t, $p < .05$). Also noteworthy, the standard deviations of amplitude measures were marginally significantly higher ($p < .10$) in the higher urine mercury group. The Levene (1960) robust test for equality of variances was used in comparing standard deviations. (Note that the same standard deviation pattern was evident in simple exposed - control group comparisons of Table 6-3.) Since tremor amplitudes cannot be less than zero, the finding that standard deviations of amplitudes are higher among exposed subjects may indicate that some of the exposed subjects had the very highest tremor amplitudes. Therefore, detailed analysis of the distribution of tremor amplitudes may be far more important than comparisons of means and standard deviations.

Figure 6-4 shows the histograms of average absolute acceleration tremor amplitudes, (AAMP) comparing the exposed and control groups. The figure shows that the exposed group did have more individuals with extreme tremor amplitudes. The exposed group showed acceleration tremor amplitudes as large as 350 mm/sec^2, compared to a maximum of 180 mm/sec^2, for the control group. Note that three subjects in the exposed group had the most extreme tremor amplitudes in excess of 220 mm/sec^2. The previously noted larger standard deviation of amplitudes among exposed subjects was mostly due to these three subjects' results. The upper 95% control limit for the control group is approximately 140 mm/sec^2. Five of the controls (2%) had tremor amplitudes exceeding 140 mm/sec^2. The exposed group, in comparison, had

12 out of 229 subjects (5%) with tremor amplitudes above 140 mm/sec. Thus, the exposed group had more than twice as many subjects above the 140 mm/sec^2 limit.

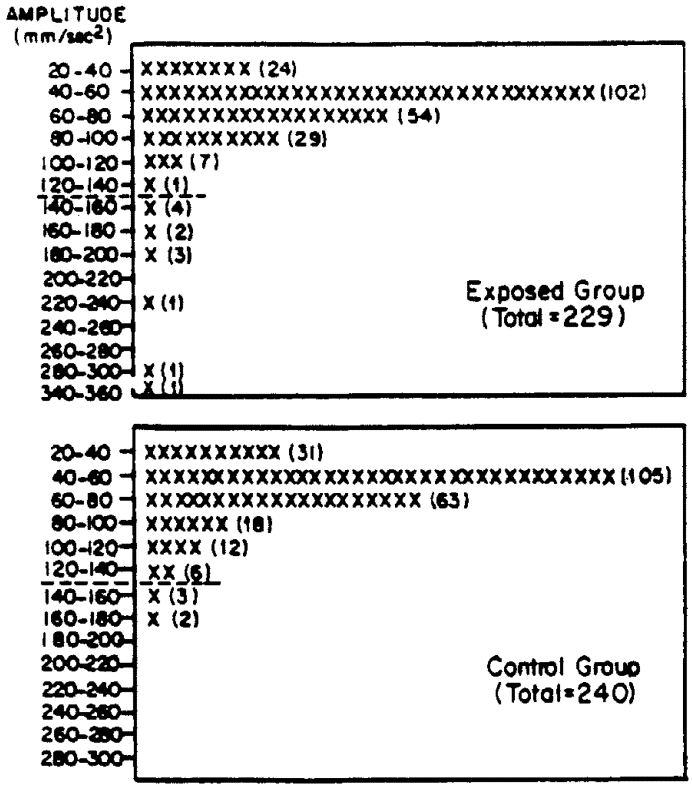

Figure 6-4. Comparison of Tremor Amplitudes (AAMP) of Exposed and Control Groups. (The dotted lines represent the upper 95 percent confidence limit of the control group.)

Grouping subjects on the basis of peak urine mercury levels resulted in a more distinct differentiation based on the quasi-arbitrary acceleration amplitude control limit of 140 mm/sec^2. Figure 6-5 compares the distribution of acceleration tremor amplitudes for the group of workers whose urine mercury histories showed one or more peaks over 0.6 mg Hg/L and the distribution of the remaining group consisting of exposed with no peaks above 0.6 mg/L including controls. The overall distributions of the two groups may be marginally significantly different using the conservative - non-parametric Mann-Whitney U test as a basis for comparison ($p = .14$). However, comparison of the high tremor amplitude tails of the distributions revealed a possibility of a more distinct

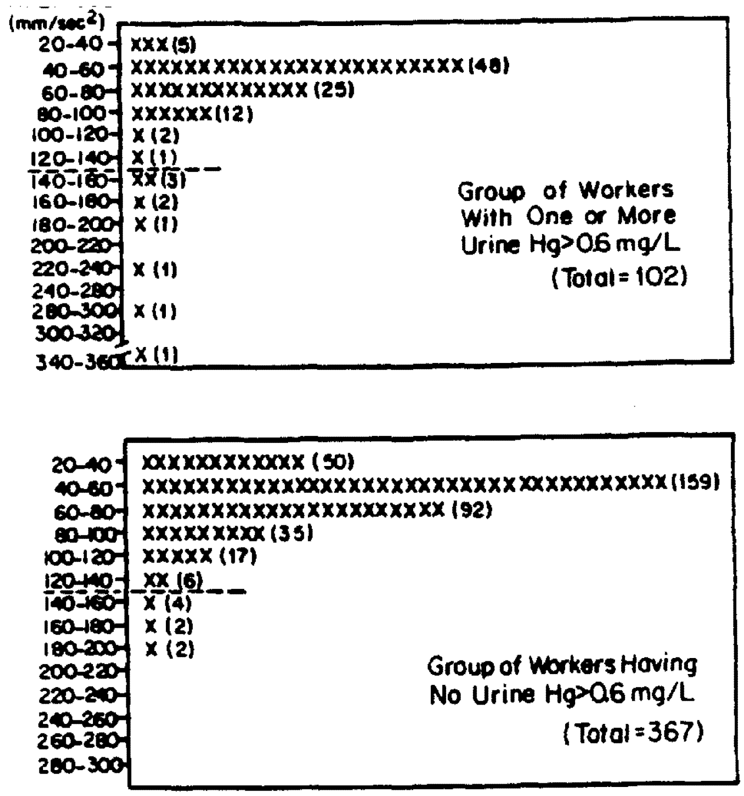

Figure 6-5. Comparison of Tremor Amplitudes (AAMP), Groups Based on Peak Measure of Urine Mercury. (The dotted lines represent the upper 95 percent confidence limit of the control group.)

difference between the highly exposed group and the comparison group. As shown in Figure 6-5, 9 out of 102 subjects in the higher urine mercury group had tremor amplitudes over 140 mm/sec^2 compared with 8 out of 359 in the comparison group. Thus, 10 percent of the group with urine mercury peaks above 0.6 mg/L had tremor amplitudes over 140 mm/sec^2, compared to only 2 percent of the larger reference group (Fisher's Exact Test, $p < .001$, Table 6-4).

In Table 6-4, the two groups of subjects did not significantly differ in mean age, education, or alcohol consumption (Student's t, $p > .20$), or in proportions of subjects with hypertension, reported drinking problems, or diabetes (Fisher's Exact Test, $p > .20$). Therefore, there is no reason to believe confounding with some other factor caused the statistically significant tremor effect associated with subjects who had urine mercury peaks over 0.6 mg/L.

TABLE 6-4: Subjects' tremor Classification versus Peak Urine Mercury History.

Tremor Class	PEAK Urine Hg<0.6 mg/L	PEAK Urine Hg >0.6 mg/L
Tremor amplitude ≤ 140 mm/sec^2	359	93
Tremor Amplitude >140 mm/sec^2	8 (2%)	9 (10%)

One must note that the number of subjects with high amplitude tremor in Table 6-4 is very small. In addition, the control limit for defining high amplitude tremor was rather arbitrarily chosen as the upper 95 percent confidence limit for the control group. Therefore, the true statistical significance of the result may be overstated because of the small number of subjects involved. As previously noted, simply testing for an overall difference between the two distributions of Figure 6-5 using the Mann-Whitney U test, a statistically more conservative approach, results in p = .14.

Acceleration Tremor Regression Analysis. The previously described tremor distribution analyses do not consider potentially important effects of variables such as age and alcohol consumption on tremor. Therefore, stepwise multiple regression analysis was used to adjust for effects of such covariates, and to examine for a dose-response relationship.

Stepwise forward regression analysis and correlation analysis were used to identify those subject related covariates that had a significant influence on tremor amplitude. Those variables that were significant ($p < .05$) included age, educational level in years,[2] and whether or not the

[2]Age and educational level were significantly correlated ($r = -.26$, $p < .001$). While age has a plausible effect on tremor amplitude, part or all of the reported effect of education on tremor may, in fact, be due to age.

subject reported having had a "drinking problem" on the medical questionnaire. ("Drinking problem" was a 0, 1; no, yes variable, Table 6-5). These three variables were used as covariates in subsequent regression analyses employing several values based on the urine mercury histories. The variables that did not have a significant association with tremor amplitude included reported current caffeine consumption, reported alcohol consumption (drinks per week), reported hypertension, diabetes, or history of lead exposure. These variables were not used in further regression analysis.

The results of regression analysis of the RMS and average absolute acceleration tremor amplitudes presented in Table 6-5 produced results that are representative of results using other amplitude measures.[3] The regression analyses of the RMS and average absolute levels were log transformed to normalize the distributions.

The partial correlations indicate consistently positive associations between urine mercury values and acceleration tremor amplitudes. However, the regression trends are only significant with values that measure the highest peak urine mercury levels: the subjects' number of levels exceeding 0.6 mg Hg per liter, and subjects' highest peak urine mercury level. Thus, the regression analyses are consistent with the previously described distribution analysis of tremor acceleration amplitude.

Exploring the nature of the highest urine mercury-tremor correlation in Table 6-5, Figure 6-6 shows the bivariate scatter relationship between subjects' highest urine mercury level in mg/L (HGPEAK) and average absolute acceleration tremor amplitude (AAMP). The corresponding bivariate regression equation is as follows:

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[3]The measures of tremor <u>frequency</u> were not significantly correlated with any urine mercury value, or with any of the covariates.

TABLE 6-5: Summary of Regression Analysis of Tremor Amplitude Variables.

INDEPENDENT VARIABLES	PARTIAL CORRELATION COEFFICIENTS WITH THE TREMOR AMPLITUDE VARIABLES	
	ACCELERATION RMS	ACCELERATION AVG. ABS. (AAMP)
Urine Mercury History Variables:		
Control-Exposed Status (0,1)	+.05	+.06
Duration of Exposure (quarters)	+.04	+.05
Integrated Urine Mercury (Sum of all quarterly values)	+.07	+.08
Number of Peak Levels above 0.3 mg/L in Entire History	+.04	+.04
Number of Peak Levels above 0.6 mg/L in Entire History	+.11*	+.12*
Peak Level (Highest Urine Hg Level for the Individual)	+.13**	+.13**
Average Urine Mercury	+.07	+.07
Covariates: (See note below)		
Age (years)	+.22***	+.22***
Educational Level (years)	-.13**	-.13**
"Drinking Problem" (0,1)	+.09*	+.09*

significance levels:

* $p < .05$
** $p < .01$
*** $p < .001$

Note: Correlation coefficients for covariates are representative results from the regression equations using the Control-Exposed Status mercury variable.

$$\log (AAMP) = 1.763 + .0490 (HGPEAK).$$

$(p = .01)$

The apparent relationship between peak urine mercury and tremor is enhanced by using multiple regression to correct for effects of other factors such as age:

$$\log(AAMP) = 1.541 + 0.504 \times 10^{-1} (HGPEAK) + .490 \times 10^{-2} (AGE)$$
$$-0.806 \times 10^{-2} (EDUCATION) + 0.836 \times 10^{-1} (DRKPRB).$$

$(p < .005$ for HGPEAK, s.d. of regression = .16, multiple r = .31)

In the multivariate regression, the association between subjects' peak urine mercury (mg/L) and acceleration tremor amplitude is statistically significant at $p < .005$. Log (AAMP) is also significantly related to age ($p < .0001$) and education ($P < .01$). DRKPRB is a variable where a value of 1 was assigned to each of the 15 subjects who reported having had an alcohol problem and is related to log (AAMP) at $p < .05$.

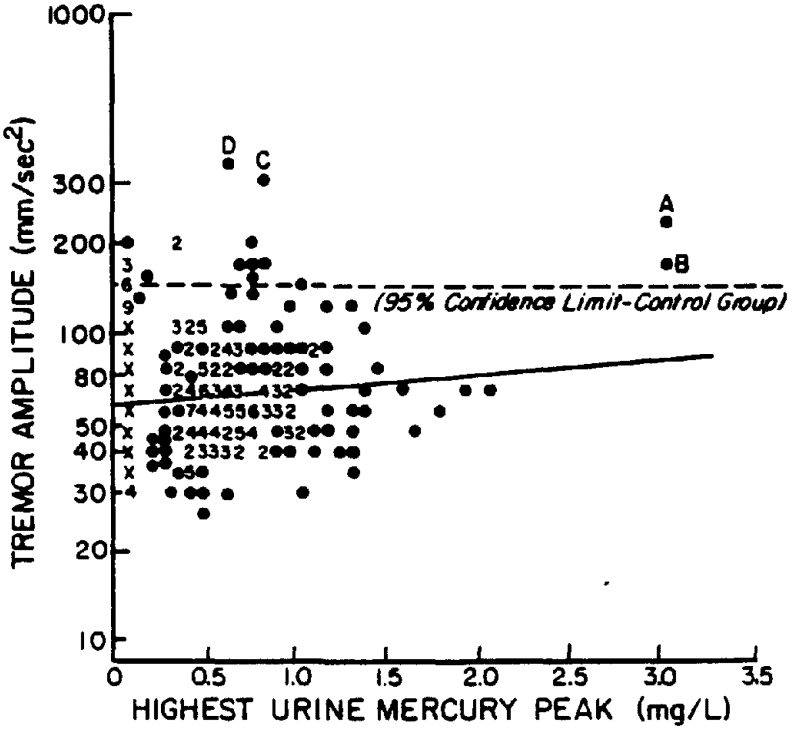

Figure 6-6. Scatter Relationship between Subjects' Peak Urine Mercury Levels and Average Absolute Acceleration Tremor Amplitude. (Numbers on graph indicate the number of subjects at each grid point. "X" means 10 or more subjects: one subject is shown as a ".".)

Figure 6-6 shows that as few as two subjects could have influenced regression results. If subjects A and B were removed from the analysis, the regression relationship between peak urine mercury and tremor amplitude would no longer be significant ($p > .20$). Likewise if subjects A, B, C, and D were removed, the resulting regression would not be at all significant ($p > .50$).

Inspection of medical examination results and questionnaires revealed no reasons for the large amplitude tremors of subjects A, B, C, and D. Subject C was a non-insulin-dependent diabetic, but this should not cause tremor. In the whole group of subjects there was no relationship between diabetes and tremor amplitude.

A statistically significant relationship was also found between the number of urine mercury peaks above 0.6 mg/L (PEAKS > 0.6) and acceleration tremor amplitude (AAMP). The regression equation is as follows:

$$\log(\text{AAMP}) = 1.543 + .235 \times 10^{-1} (\text{PEAKS} > 0.6) + 0.497 \times 10^{-2} (\text{AGE}) - 0.798 \times 10^{-2} (\text{EDUCATION}) + 0.751 \times 10^{-1} (\text{DRKPRB}).$$

($p < .002$ for PEAKS > 0.6, s.d. of regression = .16, multiple r = .31)

The mercury-related slope coefficient as is apparent in Figure 6-7 is small, but it is significant at $p < .002$. If the previously noted subjects (A, B, C, and D) were eliminated from the analysis the mercury related trend would not be significant ($p > .50$).

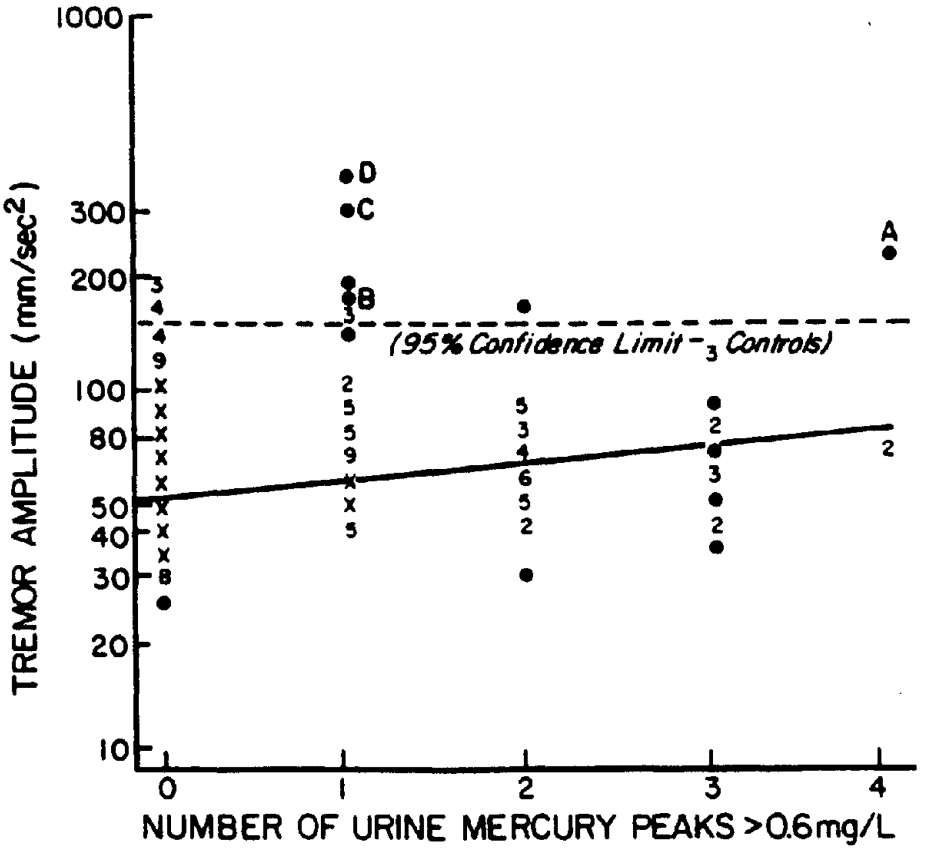

Figure 6-7. Scatter Plot of Acceleration Tremor Amplitude versus Subjects' Numbers of Urine Mercury Peaks over 0.6 mg/L. (Numbers on graph refer to number of subjects at each grid point. "X" means 10 or more.)

Age and Exposure Interaction: Older exposed subjects are more likely to have mercury related tremor. The regression analysis of the previous section showed a strong trend toward increased average absolute acceleration tremor amplitude as a function of age ($p < .0001$). Further analysis shows that the age-related tremor effect must be further qualified. In the absence of a history of mercury exposure, acceleration tremor amplitude increased very little with advancing age. As shown in Figure 6-8, the mean tremor amplitude of the control group increased only 20 percent across the decades between 50 and 90, and this small trend was statistically non-significant at

p > .25. The exposed group, on the other hand, showed a much more pronounced trend toward increasing tremor amplitude with advancing age. While the 50 to 59 year old exposed subjects had the same mean tremor amplitude as 50 to 59 year old controls, the exposed group showed a much more pronounced and statistically significant trend toward increased mean tremor amplitude in the decades beyond 60 ($p < .02$). (Analysis of covariance was used to determine the statistical significance of age related tremor trends. The mean tremor amplitudes shown in Figure 6-8 were corrected for effects of the covariates: educational level, and the indicator variable based on whether or not the subject reported having had a "drinking problem." The exposed and control groups were formed after removing the previously described 22 subjects who had motor abnormalities that could potentially confound the analysis.)

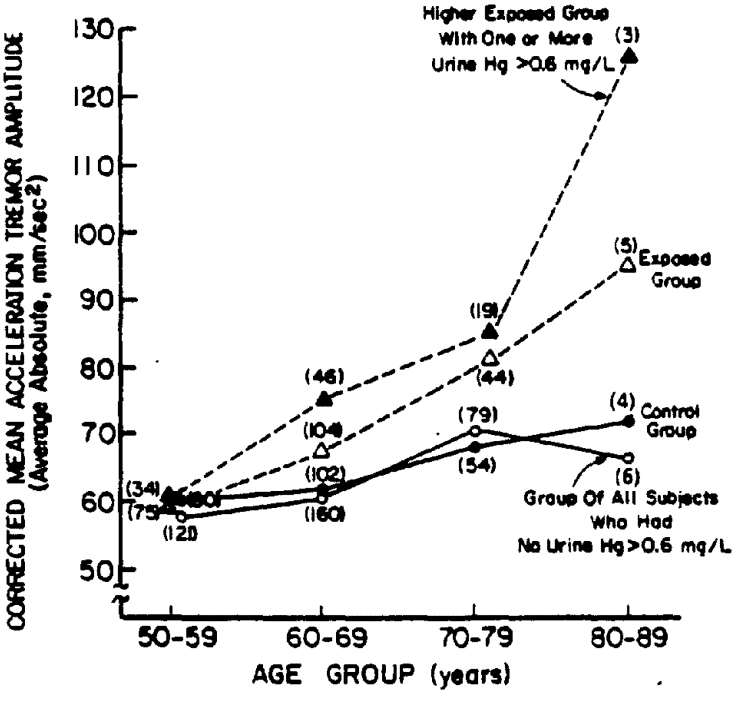

Figure 6-8. Relationship between Mean Acceleration Tremor Amplitudes for Various Exposure Categories. Amplitudes corrected for effects of educational level and reported history of drinking problem. Numbers in parentheses refer to subject sample sizes in each age - exposure category.

The foregoing control-exposed comparison may not be maximally sensitive because many of the exposed subjects had low levels of mercury exposure. Therefore as in past analyses, the higher exposed group of subjects who had peak urine mercury records over 0.6 mg/L were compared to the group of subjects who had no such records (lower exposed plus controls).

Figure 6-8 shows that the higher exposed group with urine records above 0.6 mg Hg/L had a large age-related trend toward increased tremor amplitudes in excess of the overall exposed group. For subjects aged 50 to 59 the higher exposed group had the same mean acceleration tremor amplitude as the control group, about 60 mm/sec^2. However, the higher exposure group showed an age-related progressive increase in mean tremor amplitudes reaching 126 mm/sec^2 in the 80 to 89 age range, compared to 72 mm/sec^2 for the 80-89 year old controls.

Figure 6-8 also shows that the group of lower exposed (urine Hg < 0.6 mg/L) plus controls had tremor amplitudes that were the same as controls alone. This, of course, suggests that lower mercury exposure that did not result in urine mercury over 0.6 mg/L had no effect on subjects' mean tremor amplitude in any age bracket.

One might speculate that the older exposed subjects had selectively greater tremor because they were more heavily mercury exposed in earlier periods of employment. However, the urine mercury data show that older workers had the same or possibly lower levels of exposure than younger workers. Within the exposed group the correlations between age and the six urine mercury indexes ranged from r = -.02 to -.12 (r of -.13 is significant at p = .05). Table 6-6 shows exposed subjects' urine mercury history statistics and exposure durations as a function of age. It is evident that there are no trends toward higher integrated or peak urine mercury with increasing age, nor is there a trend where older subjects had longer duration of exposure.

TABLE 6-6: Exposed Group's Mean Urine Mercury Indexes as a Function of Age.

AGE GROUP	n	INTEGRATED URINE MERCURY (mg/L)	PEAK URINE MERCURY (mg/L)	EXPOSURE DURATION (QUARTERS)
50-59	80	3.80	0.63	21.3
60-69	107	3.51	0.67	21.1
70-79	45	3.52	0.60	21.4
80-89	5	3.48	0.71	17.0

The exposed group's accelerated trend toward greater tremor with advancing age may have been largely dependent on the extreme results of a few subjects. Figure 6-9 compares individual subject's results for the control group versus the group of exposed subjects who had one or more urine mercury records in excess of 0.6 mg/L. Each data point represents a particular subject's average absolute acceleration tremor amplitude corrected for statistical effects of educational level and reported history of problem drinking. As shown in the bottom panel of Figure 6-9, the control group showed little trend in mean corrected tremor amplitudes related to age, but also all individual subject's tremor amplitudes were well contained in a band below 180 mm/sec^2. In the top panel showing results of subjects with urine mercury histories over 0.6 mg/L, however, the strong trend toward larger mean tremor amplitudes with age may be largely due to four subjects in the 60-79 year age range who had tremor over 200 mm/sec^2. These are the same four subjects, A., B, C, and D that were identified in previous analyses as having large tremor amplitudes in combination with high urine mercury history indexes.

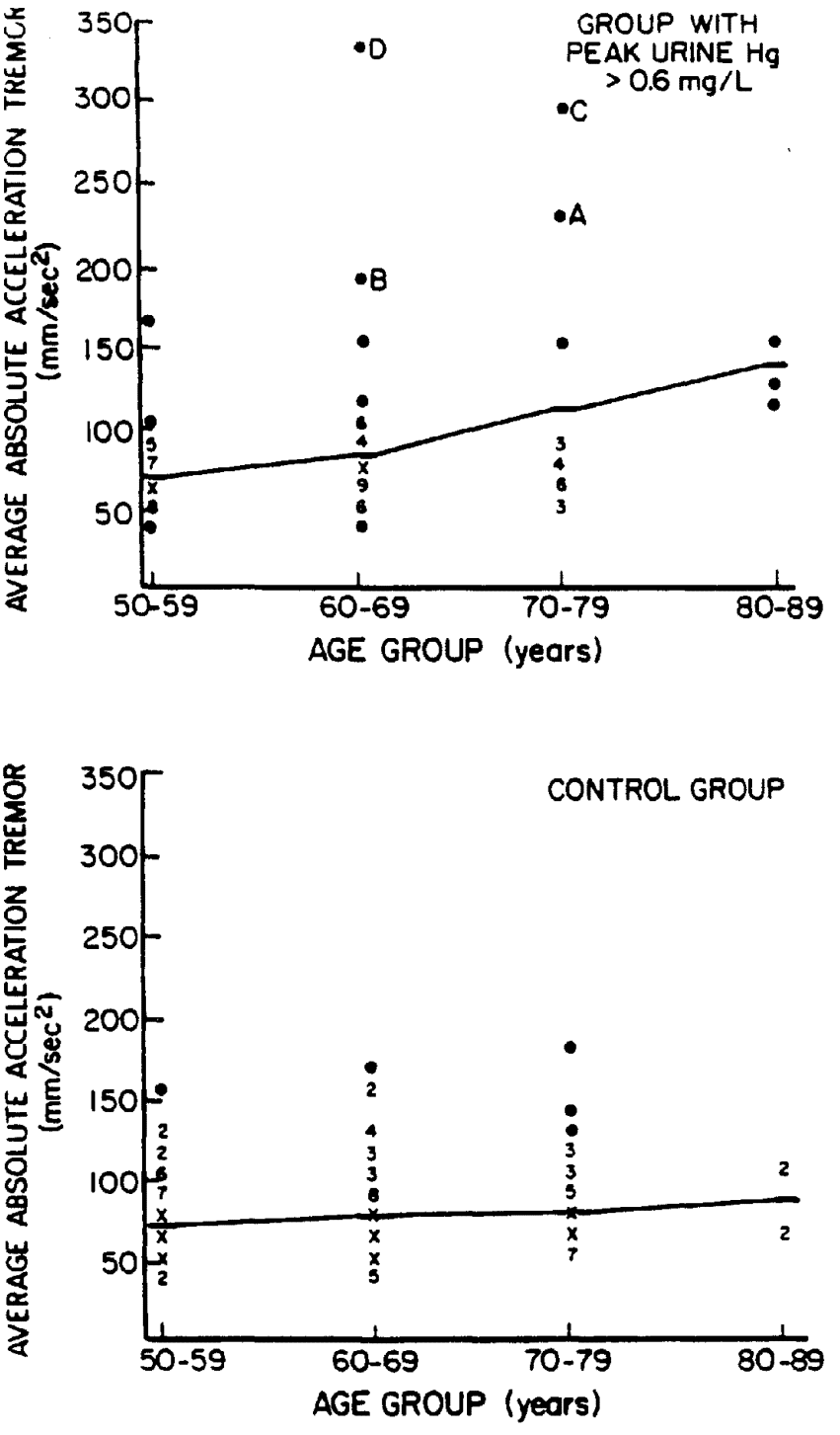

Figure 6-9. Comparison of Individual Subject's Acceleration Tremor Amplitudes: Control Group versus Group with History of Urine Mercury Peaks over 0.6 mg/L.

Discussion: Aging unmasks prior subclinical neurotoxic damage? This age x exposure interaction suggests an important qualification to the earlier observation that there probably are residual tremor effects among some of the subjects who had highest mercury exposure. It is only the older (over 60) portion of the more highly exposed group that shows a significant trend toward higher tremor amplitudes. The 50 to 59 year old higher exposed group showed a distribution of tremor amplitudes that was virtually identical to that of the control group. In the decades beyond age 60, however, the exposed groups showed an age-related increase in mean tremor amplitudes that significantly outpaced the age-related tremor amplitude trend of the control group. Further, the excessive mean tremor amplitude trend of the more highly exposed group may have been due to a few older individuals with very large tremor amplitudes.

The tendency toward significantly larger tremors among older exposed subjects did not come about because their earlier work exposures had been higher. Older exposed subjects had urine mercury histories and durations of exposure that were the same or smaller than younger exposed workers. Of course, the older subjects were also older during their periods of past work exposure, and one might speculate that older workers were more sensitive and likely to have developed exposure related tremor that did not reverse in the years between their work exposure and this study. However, there is no evidence from past studies that older mercury exposed workers show a greater tendency toward neurotoxic effects than younger, if they are observed during their periods of exposure (Farver et al. 1983; Langolf et al. 1978, 1981; Roels et al. 1985; Verberk et al. 1986).

One final hypothesis is most interesting: aging can unmask residual subclinical damage due to mercury exposure. It is possible that younger mercury exposed individuals may have some neurotoxic damage to their

neuromotor systems, but this is not revealed in tremor because of effective redundancy or compensatory mechanisms. As aging progressively reduces the capacity of compensatory mechanisms, the prior subclinical neurotoxic damage in some individuals may be unmasked and manifested in increased tremor. (In other words, neural compensatory mechanisms can deal with aging, they can deal with minor neurotoxic damage; but they may not be able to deal with both. This hypothesis could be tested in a longitudinal study of the exposed group in comparison to the control group. If the aging/unmasking hypothesis is true, then the exposed group over subsequent years should show an increased incidence of abnormal tremors compared to the control group.)

Comparison of Quantitative Tremor Amplitude and Neurologist's Rating of Tremor. Among the group of subjects who had urine mercury peaks over 0.6 mg/L, both the neurological examination and the quantitative tremor device identified a small but statistically significant excess of subjects with larger than normal tremor amplitudes. The meaningfulness of these two results would be logically enhanced if it were known that the two tremor measurement methods were consistent in identifying the same set of subjects who had above normal tremor.

Figure 6-10 shows that there was a very close relationship between the neurologists' rating of subjects' tremor and the quantitatively measured mean acceleration tremor amplitudes. However, as shown by the plus or minus one standard deviation bands in the figure, there was considerable variation in quantitative acceleration tremor within each of the neurologists' rating categories. This leaves some concern as to whether the neurologist and the quantitative device identified the same set of subjects as having above normal tremor.

Inspection of individual subject data showed that the neurologists were consistent in confirming the results of the quantitative tremor measurement.

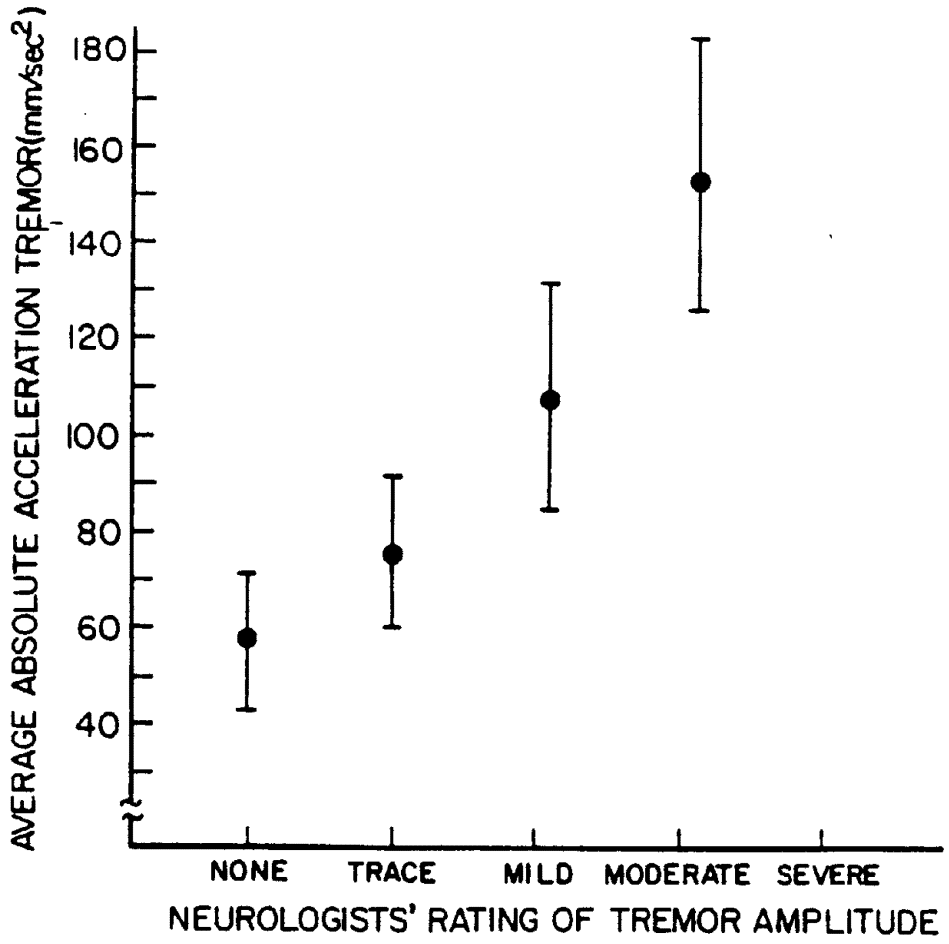

Figure 6-10. Comparison of Neurologist's Tremor Rating and Quantitative Tremor. (Bands indicate ± 1 std. dev. range.)

Of the twelve exposed subjects who had quantitative tremor amplitudes exceeding the upper 95% confidence limit, the neurologists identified eleven as having a trace or more of tremor. Three of the eleven had a "moderate" rating, the highest rating. Six had "mild" tremor, and two had a "trace." (Only Parkinsonian subjects, eliminated from this analysis, were rated "severe.")

The quantitative device results also tended to confirm the neurologists' tremor ratings. The neurologists gave twenty-one exposed subjects the highest tremor ratings of "mild" and "moderate." Included in these twenty-one were eight of the twelve subjects with the largest quantitative tremor amplitudes exceeding the 95 percent upper confidence limit. Eighteen of the

twenty-one had quantitative tremor amplitudes that were above the average of the control group.

Alternate analysis with Parkinson's disease and familial tremor cases in the sample. Since three out of four Parkinson's disease cases and two out of three familial tremor cases were formerly mercury exposed, one would expect their inclusion in the analysis to strengthen relationships between urine mercury history variables and tremor amplitude. Table 6-7 shows that such inclusion consistently increases the partial correlation coefficients

TABLE 6-7: Results of Alternate Regression Analysis, including Parkinson's and Familial Tremor Cases.

URINE MERCURY HISTORY VARIABLES	PARTIAL CORRELATIONS WITH ACCELERATION TREMOR AMPLITUDES(AVG. ABSOLUTE)	
	GROUP WITHOUT PARKINSON'S AND FAMILIAL TREMOR CASES (N = 469)	GROUP WITH PARKINSON'S AND FAMILIAL TREMOR CASES (N = 476)
Control - exposed status	+.06	+.07
Duration of Exposure	+.05	+.07
Integrated Urine Mercury	+.08	+.09*
Number of Peak Levels above 0.3 mg/L in Entire History	+.04	+.05
Number of Peak Levels above 0.6 mg/L in Entire History	+.12*	+.12*
Peak Level (Highest Urine Hg Level for the Individual)	+.13**	+.14**
Average Urine Mercury	+.07	+.09*

*p < .05
*p < .01

relating urine mercury variables and (log) tremor amplitude. However the differences are small (0.01). The pattern of correlations is the same as in the previous analyses where Parkinson's and familial tremor cases were excluded. The highest partial correlations are associated with the urine mercury variables that quantified subjects' peak levels of urine mercury. Thus, the analysis with Parkinson's and familial tremor cases included is equivalent to the previous analyses where they were excluded.

Discussion of Tremor Results. If quantitative analysis had been restricted to measures of displacement tremor that we used in our past work (Langolf et al. 1978, 1981), it is clear that there would have been no significant relationships of these tremor measures to Y-12 subjects' urine mercury values. (See Table 6-2 that shows lack of association between exposure and displacement tremor measures.) Certain European investigators have argued that acceleration tremor measures may be more sensitive in detecting changes in neuromuscular tremor, which is concentrated in the frequency bands above 4 Hz. Their argument has been supported by their recent findings of increased acceleration tremor amplitudes in subjects who had elemental mercury exposure well below current regulatory standards (Farver et al. 1983; Roels et al. 1985; Verberk et al. 1986).

Using our own new measurements of acceleration tremor amplitude, there were some statistically significant relationships between Y-12 workers' urine mercury values and their acceleration tremor amplitudes. However, these significant relationships depended on the results of a very small number of workers who had some of the very highest tremor amplitudes and also had among the highest peak values in their urine mercury histories. In analysis of the distribution of acceleration tremor amplitudes, it was found that nine out of 102 workers with peak urine values above 0.6 mg/L had tremor amplitudes that exceeded the upper confidence limit of the control

group. Using the control group as a reference, two or three would have been expected to have such high amplitudes by chance. Therefore, the most highly exposed group with urine mercury records above 0.6 mg/L had an excess of only six or seven individuals with quantitatively large tremors. (None of the exposed workers had a tremor which was rated as severe by the neurologists.)

Regression analysis showed that there were significant relationships between peak measures of urine mercury and acceleration tremor amplitude. The most significant values were the number of peaks over 0.6 mg/L, and subjects' highest peak level of urine mercury. However, it was shown that these significant regression trends were dependent on the results of only two to four individuals who were the most extreme outliers with respect to peak urine mercury and/or tremor amplitude.

The semi-quantitative measures of tremor from the neurological examination produced results which were in good agreement with the quantitative acceleration tremor measures. However, the statistical significance of the neurologist's tremor results also depended on a modest number of subjects with above normal tremor ratings. The most significant result was that 10 out of 17 workers who had three or more urine mercury peaks over 0.6 mg/L also had a neurologist's rating of a trace or more tremor. (None of these workers had moderate or severe tremors.) Using the control group as a reference, four out of the 17 would have been expected to have such tremor by chance. Therefore, an excess of only six workers with the highest urine mercury records was identified in this result.

In a sense, the tremor results of this study were similar to results of our earlier work with chloralkali workers. There, we concluded that urine mercury peaks in excess of 0.5 mg/L were most important in predicting increased tremor amplitudes, but the significance of results depended on a

very few individuals who had such high urine levels (Langolf et al. 1978). In the present Y-12 group it appears that a few individuals who had mercury exposure that ceased twenty or more years ago have mercury related tremors. Our past work showed that such tremor tended to decrease upon cessation of mercury exposure (Langolf et al. 1978, 1981). The Y-12 subject sample was carefully filtered to remove subjects with medical conditions that could contribute to tremor. In absence of any other reasons for their tremor, it is probable that about five to ten workers have a residual tremor effect due to high level mercury exposures that happened many years ago.[4] The tremor observed in most of these subjects probably has not caused any impairment. While their quantitative tremor amplitudes exceeded the control group's upper confidence limit, they were not far beyond the limit.

The analysis of an age x exposure interaction effect showed a pattern where subjects who had possible exposure related tremors were concentrated in the older age range over 60 years of age. A speculative, but interesting hypothesis follows that subclinical neurotoxic effects of mercury may be compensated, or reversed in younger subjects, but are unmasked and revealed in tremor in some older subjects because capacity of compensatory mechanisms is reduced with age-related neuronal attrition.

In summary, our finding that there were statistically significant mercury related associations could have been dependent on only a small number of subjects' results. With reference to the large majority of the 222 exposed workers that were studied, there is no evidence to suggest that there were any significant residual mercury-related tremor effects. It is probable that approximately five to ten of the most heavily exposed workers have a residual tremor related to their mercury exposure. Most of these tremors were mild in severity.

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[4]The larger estimate of 10 mercury exposed with residual tremor includes the possibility that five exposed workers with Parkinson's and familial tremor diagnoses had excessive tremor that was at least partially due to the mercury exposure.

PSYCHOMOTOR TEST RESULTS

One Hole Test

Subject Sample. Like the tremor test analysis, subjects who had medical conditions that could disrupt motor performance were removed from the analysis. These 22 subjects were previously described in the section on Tremor Test Results. (Twelve of the 22 were mercury exposed, not a statistically significant proportion.) In addition ten subjects could not perform the one-hole test well enough to produce analyzable data. Former mercury exposure was not a predominant factor in the extremely poor performance of these 10 subjects. Only two of the 10 were formerly mercury exposed. These two exposed subjects, aged 69 and 79 had integrated urine mercury indexes of 3.9 and 2.2 mg/L, not markedly different from the mean 3.6 mg/L of the exposed group as a whole. However, the 69 year old subject had one high peak urine level of 1.4 mg/L; therefore, there is a slight possibility that his inability to perform the one-hole dexterity test may be associated with a past incident high intensity exposure to mercury.

One-Hole Test - Results of Simple Comparisons and Distribution Analysis. The primary performance score was the average number of pins that the subject could insert per minute over the last four one-minute blocks of testing. This score clearly was not normally distributed and had a skewness of -0.6 and kurtosis of 3.9. Transforming by squaring each subject's raw pin score produced a distribution of scores much closer to a normal distribution with a skewness of 0.3 and kurtosis of 3.1. All statistical tests reported were performed using the squared score ($PINS^2$).

Table 6-8 shows the exposed group had a 5 percent poorer performance with a mean $PINS^2$ score of 802 versus the control group's 842, however

this difference was not significant (Student's t, p = .24)[5]. The control group had a marginally significant larger standard deviation of performance than the exposed group (Levene's robust test for equality of variances, p < .10).

TABLE 6.8 Group Comparisons of One-Hole Test Performance Scores.

ONE-HOLE PERFORMANCE PINS[2]	CONTROL GROUP n = 237	EXPOSED GROUP n = 233	GROUP WITH NO URINE Hg > 0.6 Mg/L n = 366	GROUP WITH ONE OR MORE URINE Hg > 0.6 mg/L n = 104
MEAN (STD DEV)	842 (387)	802 (346)†	833 (376)	782 (331)†

Significance of comparison:
(Levene's test)
† p < .10

The apparent reason that the control group had a larger standard deviation was that it consistently had more subjects who had high PINS[2] scores exceeding 1000 (Figure 6-11). The shaded area in the figure shows the higher proportion of control subjects with above average performance scores. A direct Mann-Whitney U test did not indicate that the two distributions were significantly different (p = .22).

Similar comparisons of the group with urine mercury records exceeding 0.6 mg/L to the group that had no such peaks produced similar results in comparing standard deviations and distributions of performance scores. However, based on attained statistical significance levels of Levene's and Mann-Whitney U tests, this method of grouping did not result in better discrimination of differences in performance on the one-hole test than simple exposed-control comparisons.

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[5]Throughout this section on tremor, psychomotor and cognitive test results, the Student t test - unpooled, unequal variance version was used to test for differences in means. In further references it will simply be called Student's t test.

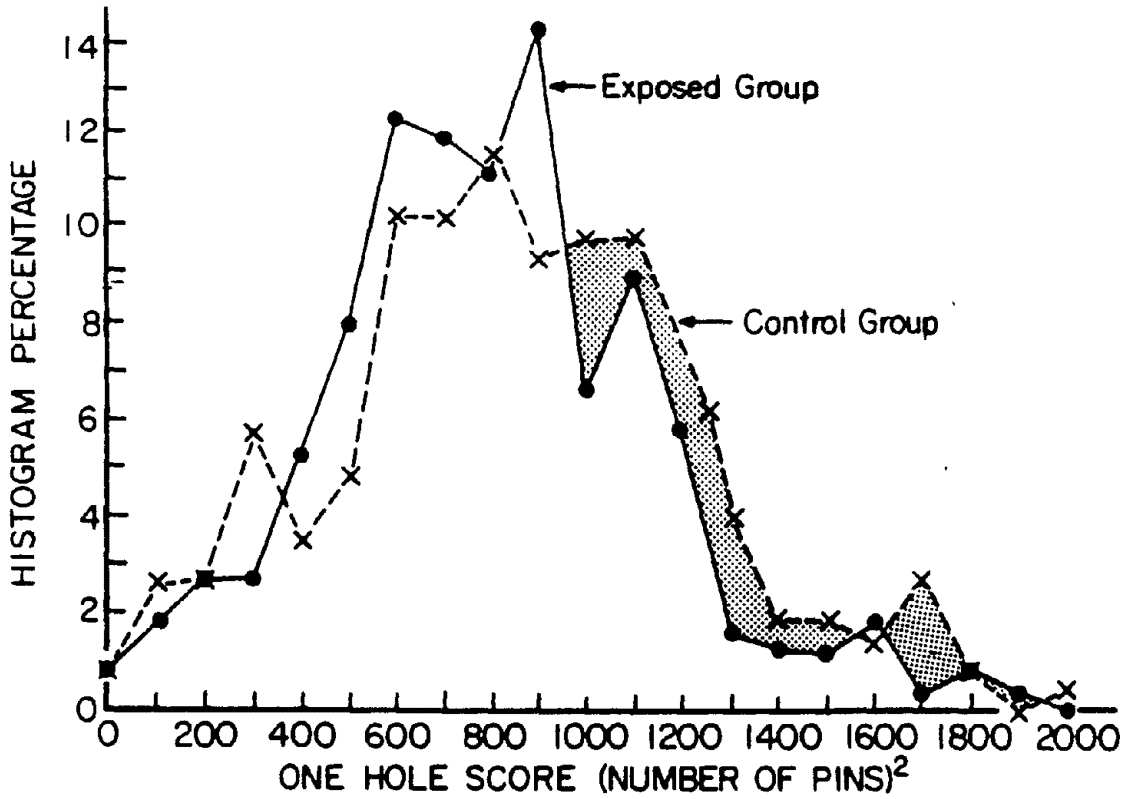

Figure 6-11. Comparison of Distributions of One-Hole Test Performance, Exposed versus Control Group. Histogram relative frequency is shown on the y axis; the midpoint of each histogram cell is shown on the x axis.

One-Hole Test - Multiple Regression Analysis. As in the quantitative tremor analysis, stepwise regression was first performed to find significant subject-related covariates that influenced the one-hole PINS^2 performance. The covariates that were found to be significant are listed below:

Age ($p < .0001$),
Education in years ($p < .01$),
Non-insulin dependent diabetes ($p < .05$),
Insulin dependent diabetes ($p < .06$).

History of lead exposure was not significantly related to one-hole test performance.

Multiple regression analysis predicting the PINS^2 score was then performed using each of the exposure variables in addition to the above covariates as independent variables. Table 6-9 summarizes the results. Consistently, the negative partial correlations indicate a trend toward poorer performance as a function of subjects' increasing urine mercury

values. With one exception, the statistically significant correlations involve urine mercury values that count or quantify peak levels (number of peaks over 0.3 or 0.6 mg/L, and the highest recorded peak level). The partial correlation with average urine mercury is also significant, but as shown earlier in this report the average measure correlates highly with all of the peak measures at r = .6 to .7. This suggests that the subjects with highest average urine mercury attained their high values through peak exposures during the short 1955-56 period of high exposure.

TABLE 6-9: One-Hole Test - Summary of Regression Analysis: Partial Correlations between Exposure Indexes and PINS^2 Score. (Negative correlations indicate poorer performance with greater exposure value.)

MERCURY EXPOSURE VARIABLE	PARTIAL CORRELATION	ATTAINED STATISTICAL SIGNIFICANCE
Control-Exposed Status	-.06	$p > .2$
Duration of Exposure (Quarters)	-.02	$p > .2$
Integrated Urine Mercury (Sum of all quarterly value)	-.07	$p > .2$
Number of Peak Levels above 0.3 mg/L in Entire History	-.10*	$p = .03$*
Number of Peak Levels above 0.6 mg/L in Entire History	-.09*	$p = .04$*
Peak Level (Highest Urine Hg for the Individual)	-.09*	$p = .05$*
Average Urine Mercury	-.10*	$p = .03$*

*$p < .05$

Figure 6-12 shows the bivariate scatter relationship between subjects' highest recorded urine mercury level and their one-hole scores. Note that subjects A and B who had the highest peak urine mercury are the same subjects who showed large tremor amplitudes. They also had below average one-hole performance scores. One might ask whether their contribution to the regression was responsible for the significant urine mercury-performance correlations of Table 6-7. Unlike the tremor results, removing these two subjects does not offset the significance of the partial correlations, and in most cases actually slightly improves the attained p level.

Including subjects A and B of Figure 6-12, the multiple regression equation is:

$$PINS^2 = 1755 - 73(HGPEAK) - 17.7(AGE) + 20.0(EDUCATION) - 104(NIDDM) - 176(IDDM)$$

($p < .05$ for HGPEAK, s.d. of regression = 333., multiple r = .44)

HGPEAK (mg/L), the highest recorded urine mercury level, is significant at $p < .05$. AGE (years) is significant at $p < .0001$; EDUCATION (years) is significant at $p < .005$. NIDDM and IDDM, the 0, 1 indicator variables for non-insulin dependent diabetes and insulin dependent diabetes, are significant at $p < .06$.

Figure 6-13 shows the relationship between subjects' average urine mercury in mg/L (HGAVE) and their one-hole scores. The corresponding multiple regression equation shows the most significant association between a urine mercury value and one-hole test performance ($p < .03$):

$$PINS^2 = 1772 - 210(HGAVE) - 17.9(AGE) - 20.0(EDUCATION) - 97.9(NIDDM) - 174(IDDM). \quad (p = .03)$$

($p < .03$ for HGAVE, s.d. of regression = 333., multiple r = .44)

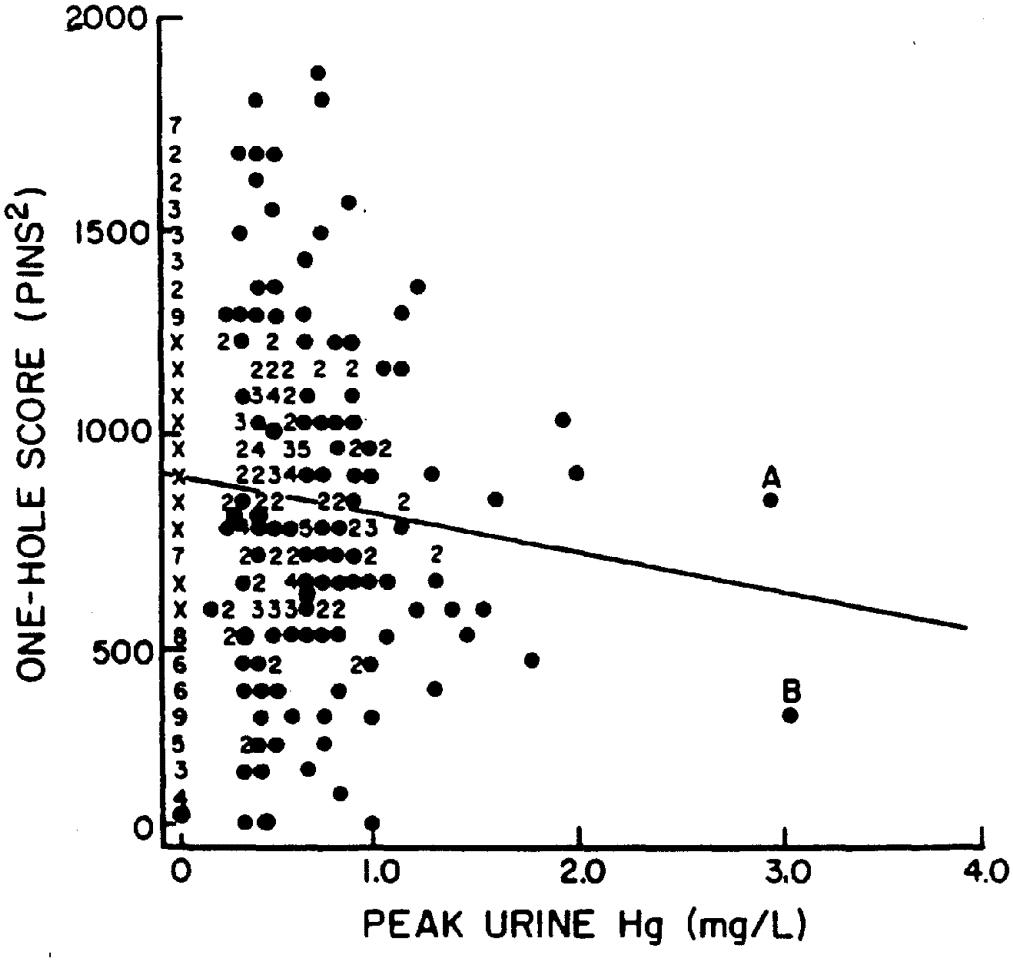

Figure 6-12. Scatter Relationship between Peak Urine Mercury and One-hole Test PINS2 score. (Numbers indicate number of subjects plotted t each grid point. "X" means 10 or more.)

Removing the two subjects with the highest HGAVE values does not affect the significance of the regression relationship. Note these two subjects shown in Figure 6-13 are not the same as subjects "A" and "B" who had the highest HGPEAK values.

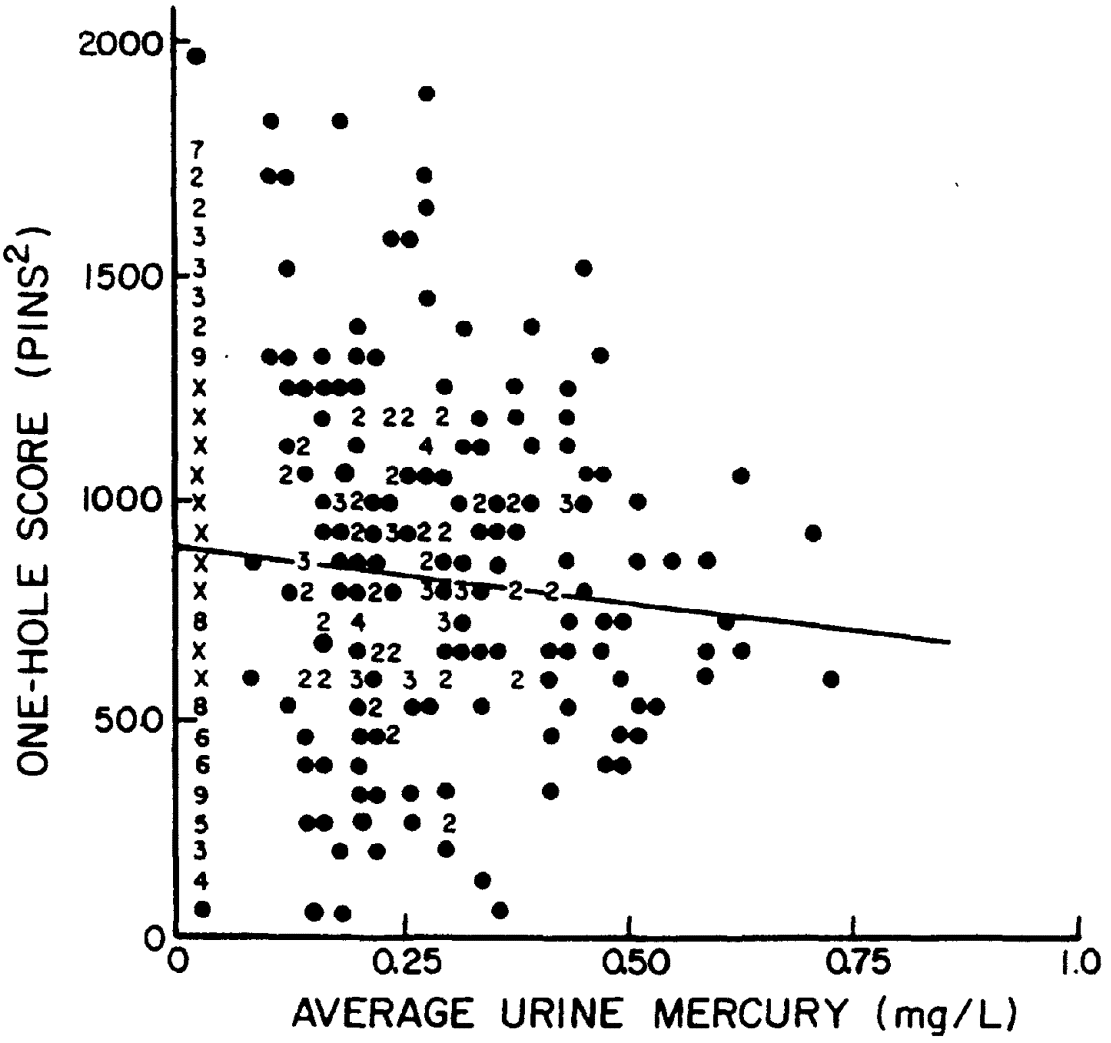

Figure 6-13. Scatter Relationship between Average Urine Mercury and PINS^2 Score. (Numbers on graph indicate the number of subjects plotted at each grid point "x" means 10 or more.)

An alternate analysis where the seven subjects who had a diagnosis of Parkinson's disease or familial tremor were included did not produce results that were substantially different from those shown in Table 6-9.

Age x Exposure Interaction Analysis - One-Hole Test. Analysis of covariance did not reveal any evidence of an age x exposure interaction effect that resembled the interaction effect noted in the quantitative tremor results. Figure 6-14 reveals no evidence of a significant divergence where older exposed or more heavily exposed subjects (urine Hg > 0.6 mg/L) had progressively poorer PINS^2 performance compared to controls.

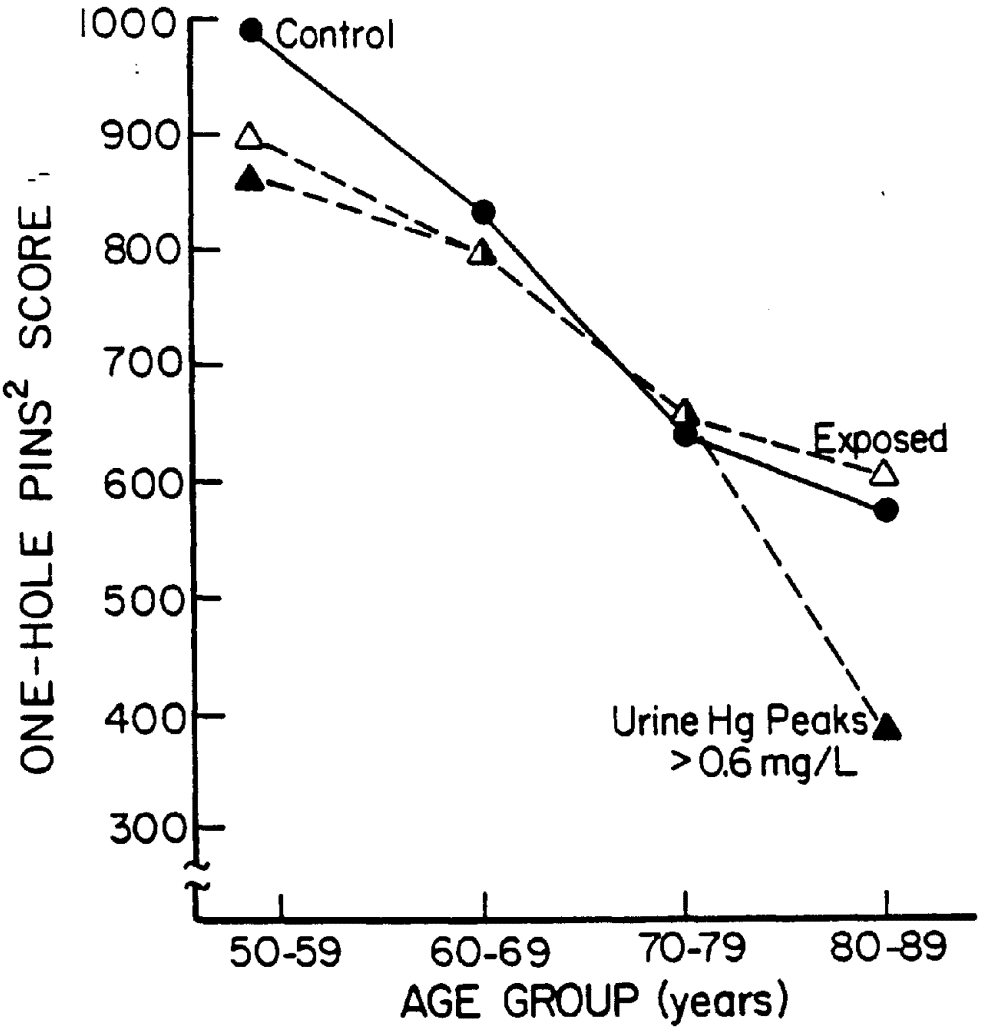

Figure 6-14. Mean PINS^2 Performance as a Function of Exposure Category and Age.

Discussion of One-Hole Test Results. The relationships of one-hole manual dexterity performance and urine mercury indexes were somewhat different than relationships found in the statistical tremor analysis. Urine mercury relationships were less significant with $p = .05$. However, the trends that were identified did not depend on the extreme results of a very small number of subjects, as they did in the tremor analysis. Rather as shown in Figure 6-11, the exposed group's distribution of one-hole test scores was consistently shifted toward lower performance (about 5 percent lower). Likewise the regression relationships of Figures 6-12 and 6-13 suggest weak but broad trends toward lower psychomotor performance with subjects'

increasing levels on urine mercury values. Overall, there is a rather weak, but significant association between subjects' past mercury exposure and slightly poorer average performance on the one-hole test of motor dexterity. The fact that urine mercury values that measured peak historical levels had the highest partial correlations with performance provides some evidence of a dose-response relationship. The average decrements in performance related to mercury on this test are small compared to the overall variation in the exposed or control population.

Simple Reaction Time

Subject Sample. As in the other psychomotor tests, 22 subjects were removed from analysis because of motor disorders detected in the neurological examination. See the section on tremor test results for the description of mercury exposure status of these subjects. Nineteen additional subjects' data were missing because they could not complete a sufficient number of right and left hand reaction trials to allow computation of a reliable composite reaction time score. Of these nineteen, only five were formerly mercury exposed, so that former mercury exposure is not a cause for the majority of poor performances. The five exposed subjects who could not complete the test had a mean integrated urine mercury index of 3.2 mg/L compared to the 3.6 mg/L mean of the exposed group as a whole. One of these five subjects had one peak historical urine level of 1.4 mg/L so there may be some cause for concern that his poor reaction time test performance may be at least partially associated with a past incident of intense mercury exposure. He was the same high exposure subject who failed to perform the one-hole test. Two other of the five exposed subjects who failed to perform the reaction time test had peak historical urine levels Of 0.8 and 1.0 mg/L, and there may be a similar concern that their poor performance could be exposure related.

Simple Reaction Time - Results of Simple Comparisons and Distribution Analysis. Table 6-10 shows that the mean reaction time of the exposed group at 378 msec.was slightly higher than that of the control group at 369 msec. This difference was marginally significant at p = .09.[6] Comparing the exposed and control groups' distribution of reaction times, Figure 6-15 shows that this was due to a consistently higher proportion of exposed subjects who had reaction times greater than 400 msec. The overall difference between the exposed and control groups' distributions of reaction times was marginally significant at p =.08 using the conservative non-parametric Mann-Whitney test.

TABLE 6-10: Group Comparisons of Simple Reaction Time Results

SIMPLE REACTION TIME (msec)	CONTROL GROUP n = 230	EXPOSED GROUP n = 228	GROUP WITH NO URINE Hg > 0.6 Mg/L n = 356	GROUP WITH ONE OR MORE URINE Hg > 0.6 mg/L n = 102
MEAN (STD DEV)	369 (53)	378† (58)	372 (55)	378 (56)

† p < .10 (Student's t for means, Levene's test for standard deviations)

Table 6-10 also shows that there was no evidence that the reaction time was progressively slower in subjects with highest urine mercury values. The reaction time parameters of the group with urine mercury peaks exceeding 0.6 mg/L were not significantly different from the group that had no urine mercury peaks over 0.6 mg/L, nor were they significantly different from those of the control group.

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[6]Prior to statistical tests reaction times were inverse transformed to normalize their distributions.

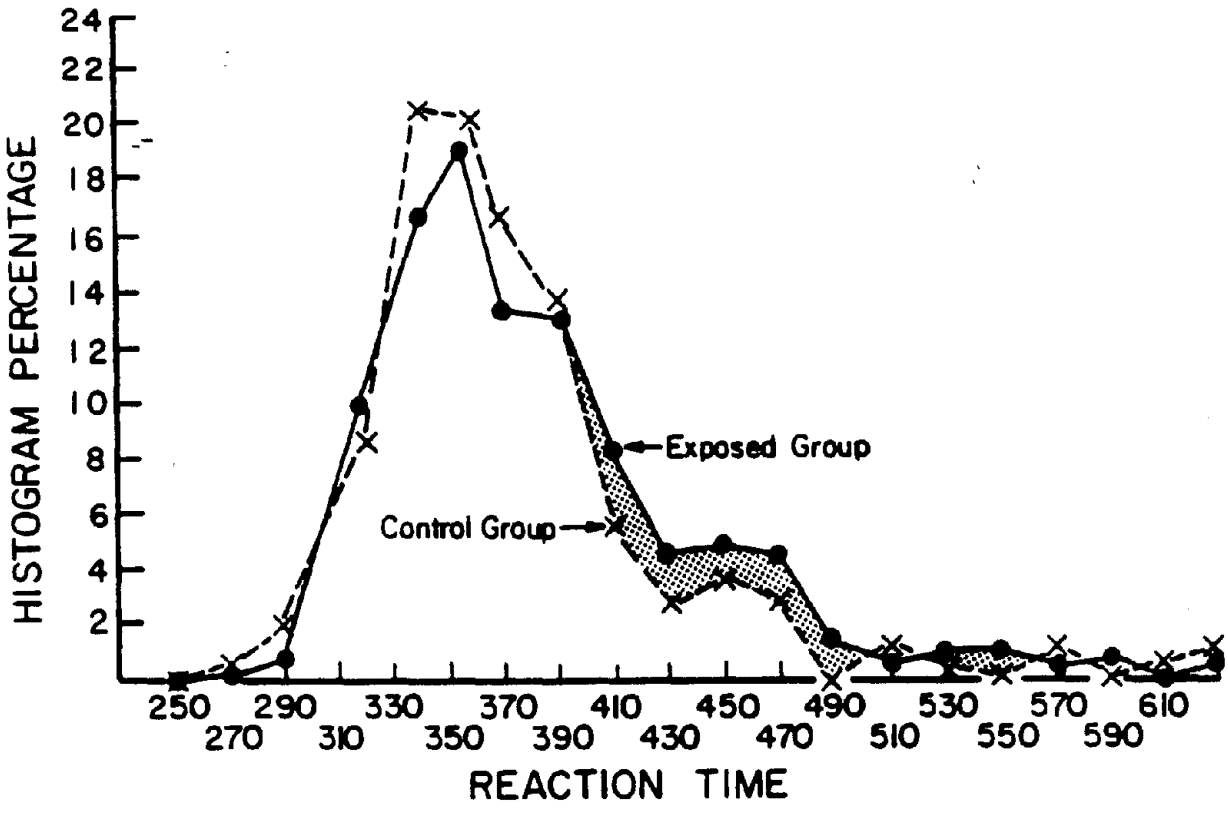


Figure 6-15. Comparison of Distribution of Reaction Times of the Exposed and Control Groups.

Simple Reaction Time-Multiple Regression Analysis. Prior to regression analysis, each subject's mean reaction time score was inverted to form a reaction speed score measured in reactions per second. This was done to normalize the scores to satisfy regression assumptions. The resulting inverse score, RSPEED, indicates better performance when it is higher. Table 6-11 gives the partial correlations between urine mercury values and RSPEED. (Multiple regression was used to correct for significant effects of age, education, and insulin dependent diabetes on reaction time. History of lead exposure had no effect on reaction time.) The table reveals little evidence of a slowing of reactions as a function of subjects' increasing intensity of past exposure as reflected in the urine mercury values. Only the peak historical urine mercury level is marginally significantly related to reaction speed ($p = .08$).

An alternate analysis which included the seven subjects with Parkinson's disease or family tremor produced partial correlations that were identical to those shown in Table 6-11.

TABLE 6-11: Simple Reaction Speed-Summary of Regression Analysis (Negative correlations indicate a trend toward slower reactions.)

MERCURY EXPOSURE VARIABLE	PARTIAL CORRELATION	ATTAINED SIGNIFICANCE LEVEL
Control-Exposed Status	-.08	p = .08
Duration of Exposure (Quarters)	-.05	p > .2
Integrated Urine Mercury (Sum of all quarterly value)	-.04	p > .2
Number of Peak Levels above 0.3 mg/L	-.03	p > .2
Number of Peak Levels above 0.6 mg/L	-.06	p > .2
Peak Level (Highest Urine in Subject's History)	-.08	p = .08
Average Urine Mercury	-.06	p = .2

Age x Exposure Interaction Analysis - Reaction Speed. As in the analysis of tremor, analyses of covariance was used to explore potential age x exposure interactions effects on reaction speed. Although the effect is not statistically significant, Figure 6-16 shows some qualitative evidence of a divergence where exposed and more heavily exposed (urine Hg > 0.6 mg/L) subjects in the older 60-69 and 70-79 age groups had selectively poorer average performance than controls. The anomalous performance of the 80-89 year old group with urine Hg > 0.6 mg/L is likely a sporadic result of having only three subjects in this age-exposure category.

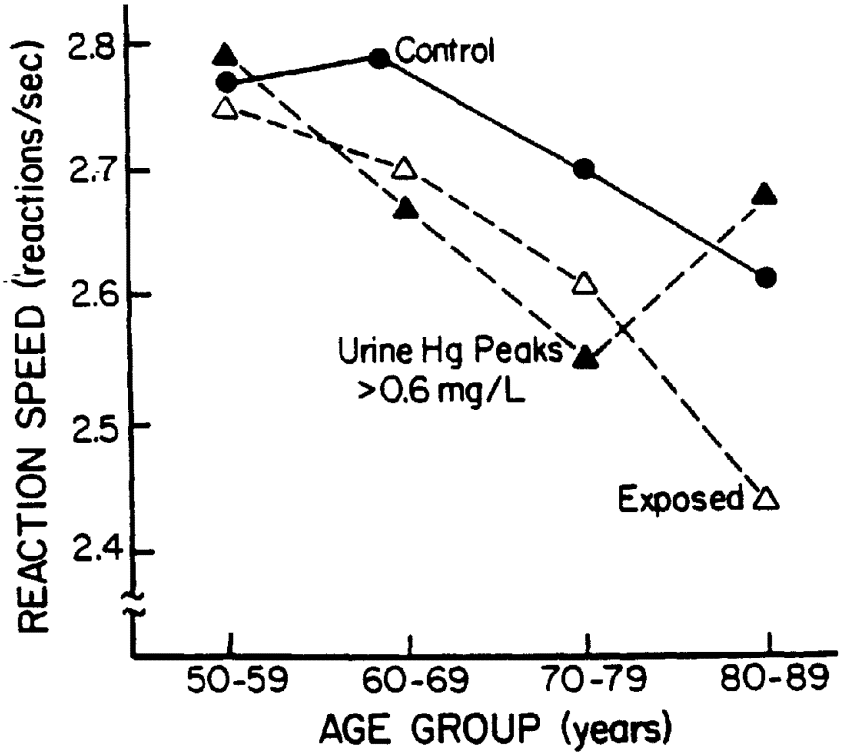


Figure 6-16. Mean Reaction Speed Scores as a Function of Exposure Category and Age.

Discussion of Reaction Time Results. While statistical tests showed that reaction times of the exposed group tended to be slower than those of the control group, there was little evidence of a dose-response relationship in that there were no large correlations between urine mercury values and slower reaction speed. The largest partial correlation was with the subjects' highest peak urine mercury level; this was only marginally significant.

Hand-Eye Coordination

Subjects. As in other psychomotor test analyses, data from 22 subjects who had motor abnormalities and diseases were excluded. (See the prior section on tremor analyses for a detailed description of these 22 subjects). In addition, eye-hand coordination test results were missing for another seven subjects because they could not perform the test well enough to produce analyzable data. Four of these seven were formerly mercury exposed, which does not indicate a significant bias toward more missing test data for exposed subjects. Two of these four formerly exposed subjects (ages 71 and

69) had higher than average urine mercury histories. Their integrated indexes were 7.3 mg and 3.9 mg; their peak levels were also high at 3.0 mg and 1.4 mg. Therefore, there may be some concern that their inability to perform the eye-hand coordination test may be related to past incidents of intense mercury exposure. Note that the second subject (1.4 mg/L peak) was the same subject who as previously noted was unable to perform the one-hole and reaction time tests.

Hand-Eye Coordination - Results of Simple Group Comparisons. Table 6-12 compares root mean square (RMS) error score parameters for the control and exposed groups. The RMS error is measured in arbitrary units. Smaller values represent better performance. The mean RMS error of the exposed group, (8.08) was 14 percent larger than control group's score (7.14). This difference in means is statistically significant (Student's t, $p < .01$). (Prior to using Student's t test, the RMS error scores were inverse transformed to normalize the distributions of scores.)

TABLE 6-12. Summary of RMS Error Scores from the Hand-Eye Coordination Test

RMS ERROR SCORE	CONTROL GROUP n = 242	EXPOSED GROUP n = 231	GROUP WITH NO URINE Hg > 0.6 Mg/L n = 370	GROUP WITH ONE OR MORE URINE Hg > 0.6 mg/L n = 103
MEAN ERROR (STD DEV)	7.14 (3.32)	8.08** (4.03)	7.45 (3.51)	8.12 (4.34)

** $p < .01$ (Student's t)

Figure 6-17 shows that nearly 30 percent of control subjects produced very low (good) RMS error scores of four. In contrast, only 19 percent of the exposed subjects had such good scores, offset by a relative excess of

exposed who had poor scores in excess of ten. The two groups' distributions are very significantly different (Mann-Whitney U, $p < .005$).

While the performance of the exposed group appears quite different from that of the control group, the results in Table 6-12 give no definite indication of a dose-response relationship. The mean RMS error score of the 103 subjects who had urine mercury peaks exceeding 0.6 mg/L was virtually identical to the exposed group as a whole (8.12 versus 8.08). Likewise the Mann-Whitney U test found no significant difference between the distribution of scores of the 103 subjects who had peaks over 0.6 mg/L and the distribution of the 353 who did not have such peaks.

Hand-Eye Coordination - Results of Regression Analysis. Before regression analysis, RMS error scores were inverted to reduce the extreme skewness (2.0) and kurtosis (5.4) of the distribution of the raw scores. The resulting inverted scores much better approximated the normal distribution, having skewness and kurtosis of 0.1 and 3.8. Multiple regression analysis employed covariates which corrected for significant effects of age, educational level and insulin dependent diabetes on hand-eye test performance. History of lead exposure had no significant regression effect on hand-eye coordination.

Table 6-13 gives the partial correlation coefficients between the various mercury exposure variables and the inverse RMS error score. The largest partial correlation was found in the relationship between simple control-exposed status (a 0,1 variable) and the inverse RMS error score ($r = .16$, $p < .001$). Of all the values, peak urine mercury shows the largest partial correlation, but this is not as large as that produced with the simple exposure status variable. Alternate analysis including Parkinsonian and familial tremor subjects revealed a similar pattern of results.

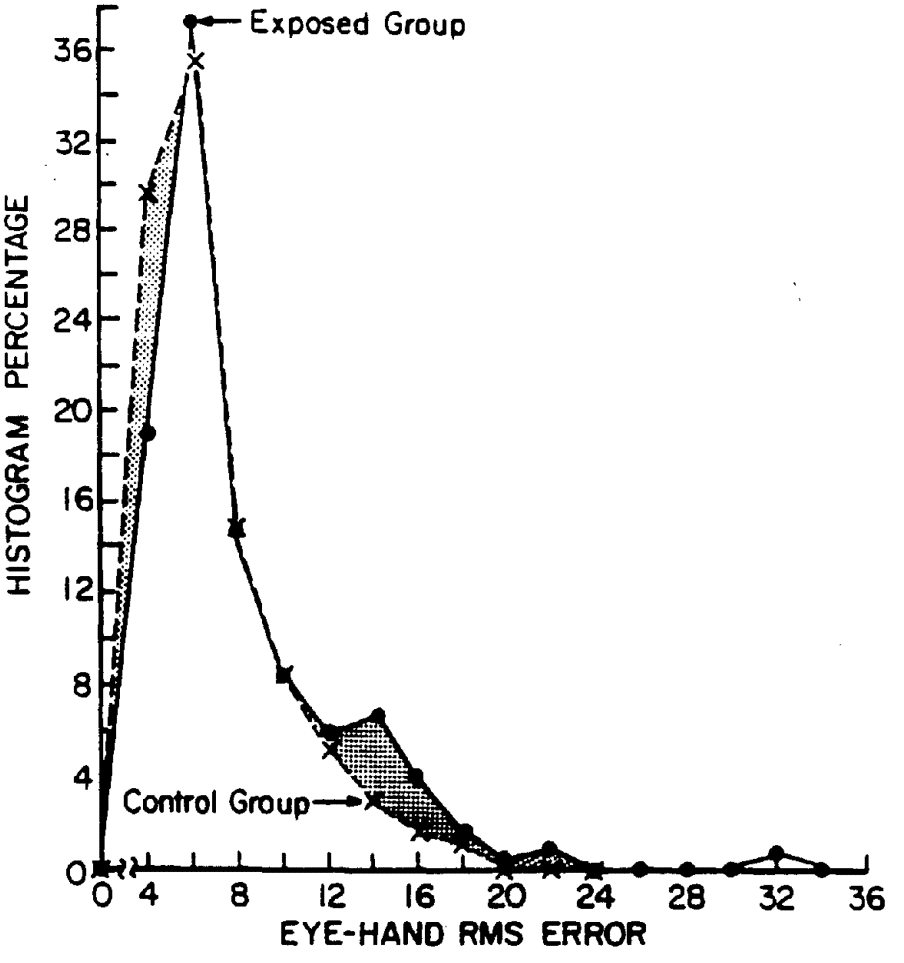


Figure 6-17. **Comparison of Control and Exposed Groups' Distributions of Hand-Eye Error Scores. (The shaded area on the left shows more controls had good scores. The shaded area on the right shows that more exposed had poor scores.)**

Age x Exposure Interaction Analysis - Eye-Hand Coordination. Figure 6-18 shows there was no evidence whatever of an age x exposure interaction effect on the inverse eye-hand coordination score. Note that the large downward trend of the control group indicates a very large aging effect on this test's performance score. The control group's trend, however, is almost exactly paralleled by the exposed and more highly exposed groups' age-related trend. The exposed group's average scores are consistently 10 to 15 percent worse than the control group's scores in every age group. This indicates a main exposure effect, but no interaction effect where older exposed subjects showed progressively poorer performance relative to the age effect in control group.

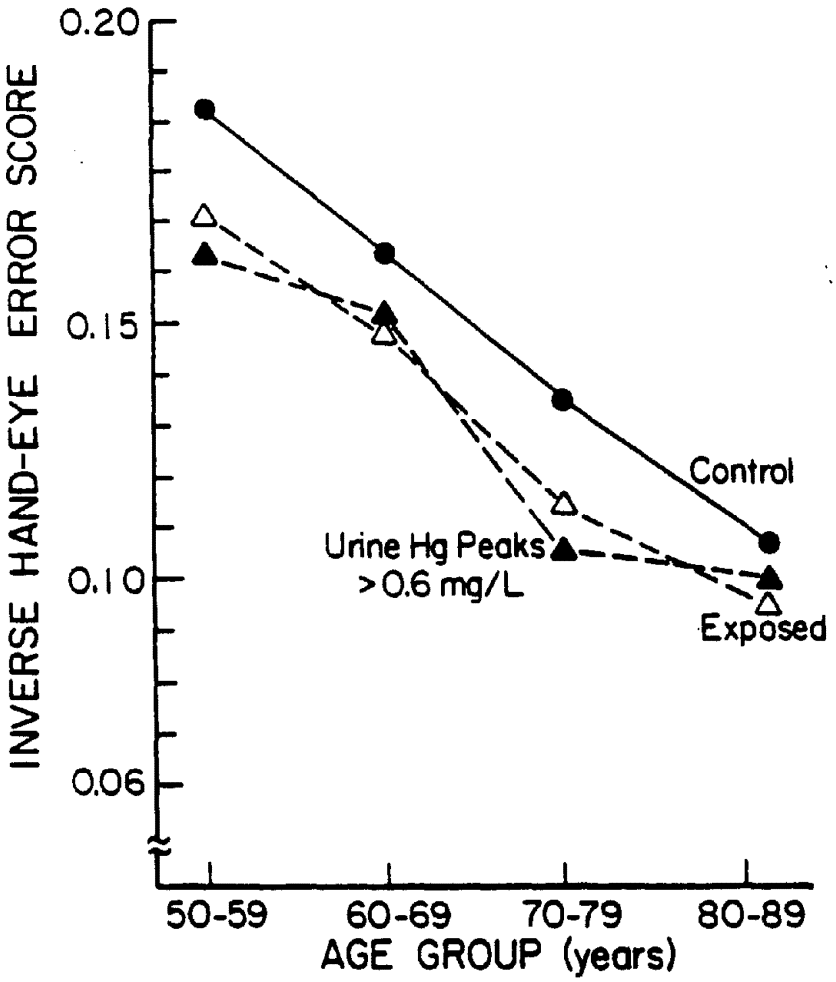


Figure 6-18. Mean Inverse Eye-Hand Coordination Scores as a Function of Exposure Category and Age.

Hand-eye Coordination - Discussion. Simple comparisons showed that the exposed group as a whole did not perform this test as well as the control group. The difference was undoubtedly significant, using three different statistical tests. While several of the quantitative measures of exposure were statistically significant predictors of poorer performance, none of the quantitative predictors was superior to simple yes-no classification of exposure. As a result we only have some support of dose-response relationship between exposure and hand-eye performance. We cannot explain why the simple exposure classification is a better predictor than quantitative urine mercury indexes.

TABLE 6-13. Hand-eye Coordination Summary of Regression Analysis. (Negative correlations indicate greater error, poorer performance.)

MERCURY EXPOSURE VARIABLE	PARTIAL CORRELATION	ATTAINED SIGNIFICANCE LEVEL
Control-Exposed Status	-.16	p = .001
Duration of Exposure (Quarters)	-.12	p = .01
Integrated Urine Mercury (Sum of all quarterly value)	-.10	p = .03
Number of Peak Levels above 0.3 mg/L	-.07	p = .12
Number of Peak Levels above 0.6 mg/L	-.08	p = .10
Peak Level (Highest Urine in Subject's History)	-.14	p = .003
Average Urine Mercury	-.13	p = .006

Summary of Tremor and Psychomotor Test Results

Analysis of tremor, one-hole, reaction time, and hand-eye test performance revealed that results of every test had some statistically significant, or marginally significant relationship to subjects' mercury exposure levels. (Only the neurologist's assessment of tremor can be clinically interpreted.)

Results of tremor analysis produced some statistically significant relationships between subjects' urine mercury values and increased acceleration tremor amplitudes. The observation that acceleration tremor was most significantly related to values of mercury peak levels supports the hypothesis of a dose-response relationship and the possible existence of a threshold. However, importantly, several of the statistically significant relationships between urine mercury values and quantitative acceleration

tremor were dependent on the results of few, possibly only two or three, subjects who had high urine mercury levels. Moreover, analyses of the age x exposure interaction strongly suggested that the subjects most likely to have a mercury exposure related tremor were concentrated among those who were both older (60 and over) and who had the highest historical levels of urine mercury (peaks above 0.6 mg/L).

Analysis of the neurologist's rating of tremor, the most clinically relevant assessment of tremor, also suggests a relationship between exposure and tremor. It is probable that approximately five heavily exposed workers had residual mild tremors as a result of high mercury exposure in the 1950's. In the entire group of the highest exposed workers only three had a moderate tremor, out of the hundred and two workers in this group. For the vast majority of the subjects exposed to either a low or high level or mercury there was no evidence of a definite tremor.

The exposed group performed about 5% poorer than the control group on the one-hole dexterity test, but the difference was not significant. Regression analysis found small but significant trends toward lower one-hole performance as a function of peak urine mercury levels, suggesting a dose-response relationship. Unlike the tremor regression results, the significance of one-hole trends was not dependent on extreme results of a very small number of subjects.

The mean simple reaction time of exposed subjects was about 3 percent slower than that of controls. The small difference was only marginally statistically significant ($p < .10$). Regression analysis failed to confirm a dose-response relationship except that a marginally significant relationship was present with the peak urine mercury value.

The hand-eye coordination test results revealed that the exposed group showed a mean error score 14 percent greater than that of the control group.

This difference was clearly statistically significant. In this test several measures of exposure were significantly related to hand-eye coordination, however the strongest relationship was for the simple no-yes exposure classification. Similarly in the regression analysis the strongest relationship was for the simple no-yes exposure classification. Thus there is not strong evidence of a dose-response relationship.

If large, functionally significant psychomotor impairments due to past mercury exposure had been present, this study's large subject sample likely would have provided highly significant and consistent evidence of dose-response relationships. Our results do not support the hypothesis that mercury exposure has caused functionally significant psychomotor impairments in a substantial number of the exposed workers. The psychomotor test results overall do indicate, that, in general, the exposed workers performed slightly poorer than did the non-exposed workers. Overall there was some evidence of a trend toward worse performance with higher exposure. These tests were not interpretable clinically. The small decrements found in these tests would not be detectable in an ordinary clinical examination and most likely do not cause clinical impairment. The combination of the tremor results and the psychomotor results together suggest that exposed subjects on average have small but clinically insignificant changes associated with their past exposure to mercury. It is likely that these changes are a residual effect of the higher mercury exposures of the 1950's. By higher exposure, we mean that those who had at least one mercury urine value above 0.6mg/L.

Cognitive Test Results

Subjects. As in the motor tests, subjects included all non-volunteers tested through September 1986. Eighteen subjects who had neurological conditions that could cause extreme results on the cognitive tests were not included in the analysis. These eighteen subjects did not significantly differ from the remaining group of subjects with respect to the proportion exposed to mercury or mean urine mercury values. Conditions that caused a subject's data to be removed from analysis are listed below:

Alzheimer's disease
Parkinson's disease
Traumatic encephalatrophy
Head injury
Heavy alcohol use
Cerebral hemorrhage or infarction
Stelazine depression
Electroshock treatment.

Nine of the 18 excluded subjects were mercury exposed. Thus, there was no bias toward excluding an excess proportion of mercury exposed subjects. The nine excluded exposed subjects had cumulative urine mercury indexes that averaged 3.1 mg/L compared to 3.6 mg/L for the exposed group as a whole. Their peak indexes averaged 0.66 mg/L compared to 0.65 mg/L for the exposed group as a whole.) These urine mercury statistics do not indicate any bias toward excluding highly exposed subjects. Four of the nine excluded exposed subjects, however, did have recorded urine mercury peaks in the 0.77 to 1.14 mg/L range, and there could be some remote concern that their medical conditions that caused exclusion could be related to past incidents of intense mercury exposure. After elimination of the 18 subjects' data, subjects who completed the various cognitive tests ranged from 246 to 252 controls, and 249 to 243 exposed.

Vocabulary and Mood Scores. From the literature on effects of mercury, there is no reason to believe vocabulary and mood are affected by low levels

of mercury exposure. These tests were used to assure that the exposed and control groups were equivalent in basic intellectual achievement (vocabulary), and equivalent in mood levels such as anxiety and anger that could affect performance on cognitive tests.

The control and exposed groups were clearly equal in vocabulary ability. Both groups had a mean score of 66% on the vocabulary test. The group of 103 highest exposed subjects who had records of urine mercury over 0.6 mg/L also had a mean vocabulary score of 66%. Regression analysis using education as a covariate did not reveal any evidence of relationships between vocabulary and subjects' urine mercury values.

The brief mood inventory given in the behavioral battery provided a score on each of five dimensions: tension, depression, anger, fatigue, and confusion. The exposed and control groups did not differ significantly in any mood dimension; likewise the group with urine records above 0.6 mg/L did not significantly differ from the control group. There were no significant regression relationships between mood scores and urine mercury values.

In summary, the subjects, regardless of mercury exposure level, were similar with respect to vocabulary ability and mood scores.

Results of Cognitive Tests - Simple Comparisons. The control and exposed groups did not differ in any comparison of short-term memory span, visual memory or symbol-digit substitution (Student's t, $p > .2$, Table 6-13). The mean cognitive test scores of the higher exposed group were not significantly different from those of the group with no urine mercury over 0.6 mg/L, or those of the control group. (The short-term memory span scores were normally distributed. The visual memory and symbol digit "percentage correct" scores were arc sine transformed to yield an approximate normal distribution. Similarly, latency scores were log transformed.)

In all comparisons of Table 6-14 it is not only clear that there are no statistically significant differences between exposed and control groups, but also that their mean test scores were virtually the same.

Cognitive Tests - Results of Regression Analysis. Regression analysis was used to explore possible relationships between the various urine mercury values and cognitive test scores. For scores other than short-term memory span, transformations as previously described were employed prior to regression analysis. Stepwise multiple regression was employed to correct for effects of age, educational level, diabetes and alcohol consumption, if

TABLE 6-14: Summary of cognitive test results.

COGNITIVE TEST RESULT	CONTROL GROUP MEAN (STD. DEV)	EXPOSED GROUP MEAN (STD. DEV.)	GROUP WITH NO URINE Hg > 0.6 Mg/L	GROUP WITH ONE OR MORE URINE Hg > 0.6 mg/L
DIGIT SPAN	5.55 (0.98) n = 242	5.45 (0.97) n = 246	5.52 (0.96) n = 367	5.54 (1.04) n = 105
VISUAL MEMORY: percentage correct	70.0 (17.8)	70.4 (18.0)	70.5 (18.0)	70.2 (17.3)
latency (sec)	8.30 (3.38) n = 239	8.29 (3.08) n = 252	8.25 (3.32) n = 370	8.27 (2.95) n = 104
SYMBOL DIGIT: percentage correct	96.8 (5.7)	97.1 (4.9)	97.0 (5.4)	97.3 (4.4)
latency (sec)	3.64 (1.22) n = 243	3.71 (1.15) n = 249	3.60 (1.12) n = 372	3.65 (1.09) n = 104

they showed statistically significant relationships to the test score under analysis. History of lead exposure showed no significant relationships with any of the cognitive test scores.

There were no significant regression relationships between any of the cognitive test scores and subjects' urine mercury values ($p > .2$). All of the partial correlation coefficients are less than .07, many were less than .05 (Table 6-15). However, there were several highly significant relationships between test scores and age and educational level. Diabetes was an important factor in reduced symbol-digit test performance. History of lead exposure, when employed as a covariate, had no significant effect on any of the cognitive test scores.

TABLE 6-15: Partial Correlation Coefficients between Cognitive Test Scores and Urine/Mercury Indexes.

COGNITIVE TEST SCORE	EXPOSURE INDEXES							COVARIATES			
	Control Exposed Status	Duration of Exposure	Integrated Urine Mercury	No. of Urine Hg Peaks over 0.3 mg/L	No. of Urine Hg Peaks Over 0.6 mg/L	Peak Urine Hg	Average Urine Hg	Age (years)	Education (years)	Non-Insulin Dependent Diabetes (0,1)	Insulin Dependent Diabetes (0,1)
DIGIT SPAN	-.01	+0.00	-.01	+0.00	0.00	-.04	-.04	-.36****	+.27****	---	---
VISUAL MEMORY: PERCENTAGE CORRECT	-0.00	+.02	-.01	-.04	-.02	-.03	0.00	-.34****	+.27****	---	---
LATENCY	+.02	+.07	+.07	+0.00	+.03	+.06	+.04	+.37****	-.19***	---	---
SYMBOL-DIGIT: PERCENTAGE CURRENT	-.04	+.03	+.03	+.03	0.00	+.02	+.01	-.17***	---	-.12*	-.15**
LATENCY	+.05	+.05	+.05	+.05	+.02	+.02	+.03	+.53****	-.29****	+.10*	---

* $p < .05$
** $p < .01$
*** $p < .001$
**** $p < .0001$

Discussion of Cognitive Test Results. Although cognitive effects of elemental mercury exposure are not as well explored as motor effects, recent studies have found relationships between elemental mercury exposure and diminished cognitive skills in subjects who were exposed at the time of testing. Smith and Langolf (1983) and Williamson (1982) found trends toward lower short-term memory capacity in concurrently exposed workers with higher levels of urine mercury. Hanninen et al. (1982) found significant relationships between elemental mercury exposure and reduced "visual intelligence" as measured by such tests as symbol-digit matching. No longitudinal studies have yet been conducted to determine if these apparent cognitive effects are reversible after cessation of exposure.

Since the urine mercury levels of subjects in the recent studies were much lower than those of Y-12 mercury workers in 1955-56, it appears probable that, if Y-12 workers had been tested in 1955-56, some would have had mercury-related cognitive effects. The present results suggest that any such mercury-related cognitive effects have not persisted.

Because of the large sample size and quality of exposed and control matching, these results can be interpreted as reasonably conclusive proof that previously mercury exposed workers have no residual decrements in the cognitive skills that were tested. Using statistical power computations for the Student's t test, this study would have detected an exposure related reduction in mean short-term memory span as small as 3.5 percent.[7] Given the recent reports of mercury-related short-term memory deficits in concurrently exposed workers, this statistic is reassuring. A failure to detect a change smaller than 3.5 percent is surely of little practical

[7]The actual means and standard deviations of test performance of the control group (Table 6-14) were used to make these power computations.

consequence. Therefore there is no reason to believe there is evidence of functionally significant short-term memory effects in the exposed group of this study.

Likewise, a change of only 1.5 percent in the exposed group's mean symbol-digit accuracy score would have almost certainly been detected; and an increase of 6 percent in response latency would have been detected (Table 6-16).

TABLE 6-16: Summary of Exposed and Control Groups' Mean Cognitive Test Results Compared to Minimum Detectable Differences.

TEST SCORE	PERCENTAGE DIFFERENCE*	MINIMUM DETECTABLE DIFFERENCE
DIGIT SPAN	(1.3%)	(3.5%)
VISUAL MEMORY:		
Percentage correct	0.5%	(5%)
latency	(0.1%)	(8%)
SYMBOL DIGIT:		
Percentage correct	0.4%	(1.1%)
latency	1.3%	(6%)

Numbers in ( ) indicate exposed group mean lower performance than control mean.

Regression analyses using urine mercury values substantiate the lack of dose-response relationships between past mercury exposure and cognitive test results. The regression results assure that there were no trends indicating dose-response relationships where only the most highly exposed workers showed residual adverse cognitive effects.

The regression results disclosed strong relationships between cognitive performance and known predictors of cognitive function, age and educational level. This helped establish the validity of the regression analysis.

7. REPRODUCTIVE HEALTH

Introduction

There are few epidemiological studies on the effects of elemental mercury exposure on the reproductive system. The reported effects from largely nonepidemiological studies include: 1) chromosomal aberrations in exposed humans and animals (Leonard, 1983; Watanabe, 1982), 2) decreased spermatogenesis and fertility in male rodents (Chowdhury, 1982), 3) transplacental passage of mercury in female humans and animals (Leonard, 1983; Kuntz, 1982), and 4) in one study, a possible association between female infertility and occupational exposure (Rachootin, 1983). These studies have raised the question of whether occupational exposure to elemental mercury may be associated with adverse effects on human spermatogenesis and pregnancy outcome. Three recent studies (HEW (NIOSH), 1979; Brodsky, 1985; Lauwerys, 1985) examining the relationship of male exposure and wife's pregnancy outcome, did not identify adverse effects.

In our analysis of the reproductive health the most important outcome measures include infertility (inability to conceive for one year or more), pregnancies resulting in miscarriage and stillbirth, major malformations in liveborn children, neonatal death and childhood illnesses.

Results

Validation of data. A randomly selected group of wives of husbands in the exposed and non-exposed groups were interviewed separately by telephone to test the quality of the data.

TABLE 7-1: Comparison of Answers Obtained from Husbands and Wives by Exposure Group

Characteristics Compared	Exposed Group (N=29) Husbands Mean(SD)	Wives Mean(SD)	paired t-test signif.	Non-Exposed Group (N=34) Husbands Mean(SD)	Wives Mean(SD)	paired t-test signif.
Number of Live-born Children	2.79(1.21)	2.83(1.17)	.33	2.47(1.62)	2.56(1.46)	.37
Number of Miscarriages & Stillbirths	0.59(1.05)	0.62(1.01)	.75	0.35(0.95)	0.44(1.13)	.26
Number of Pregnancies	3.38(1.66)	3.45(1.74)	.45	2.82(1.82)	3.00(1.76)	.16
Number of Live-born with Abnomalities[1]	0.17(0.47)	0.10(0.31)	.42	0.21(0.48)	0.0	.02
Number of Live-born with Illnesses[2]	0.31(0.66)	0.31(0.54)	1.00	0.41(0.86)	0.21(0.48)	.16

[1] Abnormalities include: Down's Syndrome, cleft palate, club foot, heart defect, kidney defect, "other".

[2] Illnesses (in childhood) include: cancer, kidney problems, nervous problems, mental retardation, small for age, surgery as child, failed grade/special education, "other".

Table 7-1 shows no statistically significant mean difference in answers provided by husbands and wives on the selected outcome variables with the exception, for the non-exposed group, of number of liveborn with abnormalities ($p = .02$). Other commonly studied pregnancy outcome variables - low birthweight and prematurity - will not be included in this analysis due to lack of agreement by husbands and wives especially on first and second born children's birthweight (child #1: $p = .006$; child #2: $p = .01$) and first born children's prematurity ($p = .002$).

Simple unadjusted comparison of exposed and non-exposed workers and their wives suggests that they are very similar in terms of personal and potentially confounding characteristics.

TABLE 7-2: Personal Characteristics and Possible Confounders by Exposure Group

Characteristics	Exposed N = 241		Non-Exposed N = 254		Test of Significance[1]
	N	Mean (SD) or Proportion	N	Mean (SD) or Proportion	p-value
Married only once (%)	241	80.9%	254	80.7%	.95+
Length of marriage	236	37.5 (9.5)	245	37.8 (9.5)	.84
Age of husband at marriage	240	24.3 (4.4)	254	24.4 (5.9)	.24
Age of wife at marriage	238	21.4 (4.3)	253	21.5 (5.3)	.54
Years of education (husband)	241	11.7 (2.5)	254	11.7 (2.6)	.91
Years of education (wife)	238	11.6 (2.2)	253	11.6 (2.2)	.83
Wives ever worked (%)	240	77.9%	254	79.1%	.74+
Wives ever smoked (%)	240	35.8%	254	40.9%	.24+
Wives ever consumed alcohol (%)	240	14.6%	253	20.9%	.07+
Wives having hysterectomy (%)	239	52.3%	253	46.6%	.21+
Husbands having vasectomy (%)	238	12.6%	252	16.7%	.20+

[1] The Mann-Whitney test has been employed except for crosstabular comparisons (+) where the Chi-Square Statistic with 1 degree of freedom has been calculated.

Eighty-one percent of the subjects have been married only once with a mean length of marriage of 38 years (Table 7-2). For both groups, most husbands and wives were married in their early 20s and have a high school

education. Slightly more than 75% of wives in both groups have worked at some point during their marriage. Less than 45% of wives have ever smoked cigarettes and less than 25% have ever consumed alcohol in either group. Fifty-two percent of wives of exposed subjects and 47% of wives of non-exposed subjects have had a hysterectomy, the majority of which was not cancer-related. Thirteen percent of the exposed and 17% of the non-exposed have had a vasectomy.

TABLE 7-3: Reproductive Outcomes by Mother and by Exposure Group

Outcome by Mother	Exposed N = 241		Non-Exposed N = 254		Test of Significance[1]
	N	Mean (SD) or Proportion	N	Mean (SD) or Proportion	p-value
Number of live-born children	241	2.4 (1.8)	254	2.5 (1.6)	.47
Number of miscarriages & stillbirths	241	0.41 (.85)	254	0.27 (.62)	.07
Total number of pregnancies	241	2.9 (2.0)	254	2.8 (1.8)	.86
Miscarriages & stillbirths/ pregnancies (%)[5]	241	12.0% (22.3%)	237	9.3% (20.6%)	.08
Abnormality/ liveborn (%)[2,5]	216	7.4% (17.5%)	232	7.3% (19.2%)	.67
Illness/ liveborn (%)[3,5]	216	11.9% (24.2%)	232	14.2% (27.1%)	.46
Infertility (%)[4]	240	12.5%	253	11.5%	.72+

1 See note 1, Table 7-2.
2 Abnormalities include: Down's Syndrome, cleft palate, club foot, heart defect, kidney defect, "other".
3 Illnesses in childhood include: cancer, kidney problems, nervous problems, mental retardation, small for age, surgery as child, failed grade/special education, "other".
4 Infertility: inability to conceive after trying for one year or more.
5 Families with no pregnancies, and in the case of abnormalities and illnesses, no liveborn children, are excluded from these analyses.

Table 7-3 presents a comparison by group of reproductive outcome measures. The two groups do not differ statistically significantly in number of liveborn, total number of pregnancies, rate of children born with abnormalities and illnesses or reported infertility. However, the exposed group has more miscarriages-stillbirths and it has an elevated rate of miscarriage-stillbirth. The difference between the groups on these two outcome measures is marginally statistically significant.

Forty-nine percent of liveborn children are males in the exposed group and 50% are males in the non-exposed group. About five percent of liveborn children in both groups are no longer alive. Most of those have died in infancy. Among liveborn children of fathers in the exposed group who are no longer alive and who have died in infancy, 4 experienced birth trauma, 3 were premature, 2 succumbed to crib death and 3 were afflicted with open spine, heart problem and pneumonia respectively. One died one half hour after birth for unknown reasons. One died at age 4 from colon cancer.

Among liveborn children of fathers in the non-exposed group who are no longer alive and who have died in infancy, 2 experienced birth trauma, 3 experienced breathing problems, and 8 suffered from pneumonia, nephritis, kidney infection, heart problems, blood problems, collapsed lung, diarrhea and stomach problems respectively. One died from Rh incompatibility and 2 suffered from unknown causes.

TABLE 7-4: Mothers Classified by Exposure and Number of Miscarriages-Stillbirths

Exposure Group	Number of Miscarriages-Stillbirths				
	None	One	Two	Three or More	Total
Exposed	175 (72.6%)	46 (19.1%)	13 (5.4%)	7 (2.9%)	241 (100%)
Non-Exposed	201 (79.1%)	42 (16.5%)	8 (3.2%)	3 (1.2%)	254 (100%)
Total	376	88	21	10	495

Chi-Square (3 d.f.) = 4.43, p = .22

Table 7-4 examines the distribution of mothers by number of miscarriages-stillbirths. In both groups most women have no miscarriages-stillbirths, but there are slightly fewer women with no miscarriages-stillbirths in the exposed group (72.6%) than in the non-exposed group (79.1%). A slightly higher fraction of women in the exposed than non-exposed group have one, two and three or more miscarriages-stillbirths. Although the overall distribution of mothers on number of miscarriages-stillbirths and husband's exposure status is not statistically significant (p = .22), the pattern suggests that the mean differences obtained in Table 7-3 for miscarriage-stillbirth outcomes are not the result of a few outliers (for example, a few women with many miscarriages in the exposed group).

Adjusted group mean comparison employs analysis of covariance to compare mean differences between groups on selected outcome variables while holding constant the effects of variables believed a priori to have an impact on pregnancy outcome (Table 7-5).

TABLE 7-5: Group Comparison (adjusted[1]): Pregnancy Outcomes by Mother

Outcome by Mother	Exposed N = 241 Adjusted Mean (SD)	Non-Exposed N = 254 Adjusted Mean (SD)	Test of Significance (covariance) p - value	(N)
Number of live-born children	2.4 (.1)	2.5 (.1)	.60	(487)
Number of miscarriages & stillbirths	0.41 (.05)	0.27 (.05)	.04	(487)
Total number of pregnancies	2.8 (.1)	2.8 (.1)	.71	(487)
Miscarriages & stillbirths/ pregnancies (%)[2]	12.0% (1.5%)	9.3% (1.4%)	.09	(451)
Abnormality/ liveborn (%)[2]	7.2% (1.3%)	7.4% (1.2%)	.72	(440)
Illness/ liveborn (%)[2]	12.0% (1.8%)	14.1% (1.7%)	.49	(440)

1 Adjusted for wife's and husband's age at marriage, wife's and husband's education, wife ever smoked and wife ever drank alcoholic beverages regularly. This reduces the available sample size from that presented in Table 7-3.

2 These outcome variables have been log-transformed to reduce skewness. Families with no pregnancies, and in the case of abnormalities and illnesses, no liveborn children, are excluded from these analyses.

Several variables have been considered, including age of wife and husband at marriage, their educational attainment, and wife's smoking and drinking history. The combined effect of the covariates do not affect the mean of the reproductive outcome variables. This is not surprising since the groups do not differ significantly in terms of these potential confounders (Table 7-2). As in the earlier analyses (Table 7-3) the difference in the mean total number of miscarriages-stillbirths and the mean miscarriage-

stillbirth rate are significant (p = .04) and marginally significant (p =.09) respectively.

Dose-response. To determine whether the possible adverse effects of exposure might be dose-related, a multiple regression technique has been employed which includes two different indicators of exposure (dose) in separate equations: the sum of mean quarterly exposure levels - HGU-LEQU - and the measure of highest peak - HGPEAK.

TABLE 7-6: Dose-Response Analysis: Pregnancy Outcomes by Mother

	HGU-LEQU Regression[1] (N = 495)		HGPEAK Regression[1] (N = 480)		
	Partial Correlation Coefficient	p - value	Partial Correlation Coefficient	p - value	(N)
Number of liveborn children	-.039	.40	.014	.76	(487)
Number of miscarriages & stillbirths	.104	.02	.085	.06	(487)
Total number of pregnancies	.007	.87	.047	.31	(487)
Miscarriages & stillbirths/ pregnancies(%)[2]	.096	.04	.068	.15	(451)
Abnormality/ liveborn (%)[2]	.012	.80	.025	.60	(440)
Illness/ liveborn (%)[2]	-.052	.28	-.017	.72	(440)

[1] Included in each regression equation are the following possible confounders: Wife's age at marriage, husband's age at marriage, wife's and husband's education, wife ever smoked and wife ever drank alcoholic beverages regularly.

[2] These outcome variables have been log-transformed to reduce skewness. Families with no pregnancies, and in the case of abnormalities and illnesses, no liveborn children, are excluded from these analyses.

In general, there is no dose-response relationship between exposure to mercury and pregnancy outcome (Table 7-6). However, for miscarriages-stillbirths and miscarriage-stillbirth rate, the partial correlation coefficients for HGU-LEQU are significant ($p = .02$ and .04 respectively) holding a priori variables constant. When predicting the same two outcomes but replacing the HGU-LEQU measure with HGPEAK, the partial correlation coefficient for HGPEAK approaches significance for number of miscarriages-stillbirths ($p=.06$) but is not significant ($p=.15$) for miscarriage-stillbirth rate.

Stepwise backward regression for the equations in Table 7-6 containing the HGU-LEQU measure and the possible confounders and predicting (A) number of miscarriages-stillbirths, and (B) miscarriage-stillbirth rate produces the following significant and marginally significant equations:

(A): No. of miscarriages-stillbirths = .23 + .12 wife smoking + .00004 HGU-LEQU

$R^2 = .02$ (SE = .74), $p = .02$;
p-value for HGU-LEQU = .03.

(B): LOG (miscarriage-stillbirth rate) = .81 + .00007 HGU-LEQU

$R^2 = .01$ (SE = 1.60), $p = .07$.

Table 7-7 complements Table 7-6. In Table 7-7 pregnancy outcomes are compared across selected HGU-LEQU dose levels: none (i.e. non-exposed), low dose (2000-3999ug/L) and high dose (4000-9000ug/L). While for most outcome variables there is no change in mean value across dose levels, the number of miscarriages-stillbirths appears to increase with increasing dose level ($p=.02$). The two methods of dose-response analysis provide some evidence of a weak relationship between exposure and miscarriage-stillbirth outcome.

TABLE 7-7: Comparison of Mean Pregnancy Outcome by Mother across Levels of Exposure[1].

OUTCOME	NONE N	NONE N = 254 MEAN (SD)	LOW (2000-3999 ug/L) N	LOW N = 166 MEAN (SD)	HIGH (4000-9000 ug/L) N	HIGH N = 75 MEAN (SD)	Test of Significance[2]
Number of liveborn	254	2.5 (1.6)	166	2.4 (1.9)	75	2.4 (1.6)	.94
Number of miscarriages & stillbirths	254	.27 (.62)	166	.36 (.74)	75	.55 (1.1)	.02
Total number of pregnancies	254	2.8 (1.8)	166	2.8 (2.1)	75	3.0 (1.8)	.65
Miscarriages & stillbirths/ pregnancies (%)[3]	237	9.3% (20.7%)	153	10.4% (20.6%)	69	15.6% (25.5%)	.06
Abnormality/ liveborn (%)[3]	232	7.3% (19.2%)	150	7.5% (17.9%)	66	7.0% (16.7%)	.88
Illness/ liveborn (%)[3]	232	14.2% (27.1%)	150	14.4% (27.2%)	66	6.1% (13.9%)	.17

[1] HGU-LEQU (N=241): Mean = 3610.4, SD = 1197.7; range = 2144.0 to 8572.0
[2] Test for the equality of means (ANOVA).
[3] p-value is based on log-transformed variables.

Pregnancy outcome as unit of analysis. In the previous analyses mother or married couple has been the unit of analysis. In the following analyses pregnancy is treated as the unit of analysis which gives equal weight to each pregnancy outcome. Outcome rates in the current analyses differ from those in previous analyses because of the change in unit of analysis from mother to pregnancy.

For each pregnancy the year in which the outcome occurs is recorded. Since it is time of conception or even pre-conception that is of interest in this type of reproductive analysis (emphasis on father's exposure), an approximation is made. With year of occurrence as the only time reference,

we arbitrarily assume it is month 6 (midway through a year) for each pregnancy outcome. Because a live birth normally follows a 9 month gestation period, we use the convention that conception occurs during the year prior to each live birth. Most miscarriages in the sample take place after 2 to 4 months of gestation. There are very few stillbirths, defined as occurring in months 7-9 of the pregnancy (8 stillbirths in the exposed group and 5 in the non-exposed group). For miscarriage-stillbirth outcome, we use the convention that year of conception is the same as year of occurrence.

Temporal Relationships: Exposure and Reproductive Outcome: Unadjusted Comparison.

The following analyses compare pregnancy outcome by exposure group and general exposure history of the plant. The Mantel-Haenszel Chi-Square statistic (Chi-Square MH) is used to assess the relationship between adverse reproductive outcome and exposure across time periods. There are five periods of interest based on the general exposure level of the plant:

A. 1952 and earlier: no exposure

B. 1953-1954: small number exposed

C. 1955-1956: period of heaviest exposure

D. 1957-1966: period of lower exposure

E. 1967 and later: very little exposure

TABLE 7-8: Miscarriage-Stillbirth Rates per Pregnancy by Exposure and Time Period[1].

Time Period	Exposed	Non-Exposed	Odds Ratio
A. 1952 and earlier	11.7% (47/401)	9.0% (38/422)	1.34
B. 1953-54	15.8% (12/76)	9.7% (7/72)	1.74
C. 1955-56	13.4% (9/67)	7.7% (4/52)	1.86
D. 1957-66	21.7% (26/120)	11.3% (15/133)	2.18
E. 1967 or later	18.2% (2/11)	25.0% (2/8)	0.67
TOTAL	14.2% (96/675)	9.6% (66/687)	1.57

Chi-Square MH (1 d.f.[2])=6.98, p=.008
Interaction effect: Chi-square(4 d.f.)=1.98, p=.74

1 Information is missing on dates for 11 pregnancy outcomes (including 4 miscarriages) and 13 pregnancy outcomes (including 3 miscarriages) in the exposed and the non-exposed groups respectively.
2 D.f.= degrees of freedom.

In this analysis the exposed group has a significantly higher miscarriage-stillbirth rate than the non-exposed group (Table 7-8). The average odds ratio for miscarriage-stillbirth is 1.57 (p=.008, Chi-Square MH (1d.f.)=6.98), and no significant interaction is observed across time period (Chi-Square (4 d.f.)=1.98, p=.74). At least half of the miscarriages-stillbirths occurred before the start of mercury exposure.

Of particular interest are the comparisons of adverse reproductive outcome between the time period when neither of the study groups were exposed (A: 1952 and earlier) vs. the period of heaviest exposure (C: 1955-56) and the period (D: 1957-66) with lower exposure and possibly a latent exposure effect. The rate of miscarriage-stillbirth by exposure group does not differ significantly across time periods A and C (Chi-Square (1 d.f.)=.12, p=.72) or across time periods A and D (Chi-Square (1 d.f.)=1.28, p=.26)(not shown). Thus, while it is evident that the exposed group has a higher miscarriage-stillbirth rate than the non-exposed group, it does not

appear that onset of exposure substantially changes the difference between the two groups in the rate of miscarriage-stillbirth.

TABLE 7-9: Rates of Children born with Abnormalities per Liveborn by Exposure and Time Period[1].

Time Period	Exposed	Non-Exposed	Odds Ratio
A. 1952 and earlier	5.1% (18/354)	6.5% (25/384)	0.77
B. 1953-54	9.4% (6/64)	12.3% (8/65)	0.74
C. 1955-56	12.1% (7/58)	14.6% (7/48)	0.80
D. 1957-66	7.4% (7/94)	7.6% (9/118)	0.97
E. 1967 or later	22.2% (2/9)	16.7% (1/6)	1.43
TOTAL	6.9% (40/579)	8.1% (50/621)	0.82

Chi-Square MH(1 d.f.[2])=0.83, p=.36
Interaction effect: Chi-Square(4 d.f.)=.31, p=.99

1 Information is missing on dates for 7 liveborn children (4 abnormalities) in the exposed group and 10 liveborn (1 abnormality) in the non-exposed group.
2 See note 2, Table 7-8.

For liveborn children with abnormalities (Table 7-9) no significant relationship is found between exposure and abnormality rate (average odds ratio=.82, p=.36, Chi-Square MH (1 d.f.)=.83), and the relationship does not vary across time period (Chi-Square (4 d.f.)=.31, p=.99).

TABLE 7-10: **Rates of Children with Early Childhood Illnesses per Liveborn by Exposure and Time Period**[1]

Time Period	Exposed	Non-Exposed	Odds Ratio
A. 1952 and earlier	9.3% (33/354)	11.5% (44/384)	0.79
B. 1953-54	14.1% (9/64)	13.8% (9/65)	1.02
C. 1955-56	10.3% (6/58)	20.8% (10/48)	0.44
D. 1957-66	16.0% (15/94)	16.1% (19/118)	0.99
E. 1967 or later	22.2% (2/9)	16.7% (1/6)	1.43
TOTAL	11.2% (65/579)	13.4% (83/621)	0.82

Chi-Square MH(1d.f[2])=1.31, p=.25
Interaction Effect: Chi-square(4 d.f)=1.78, p=.78

1 Information is missing on dates for 7 liveborn children (4 illnesses) in the exposed group and 10 liveborn (1 illness) in the non-exposed group.
2 See note 2, Table 7-8.

Finally, for liveborn children with childhood illnesses (Table 7-10), no significant relationship exists between exposure and illness (average odds ratio=.82, p=.25, Chi-Square MH (1 d.f.)=1.31) and no significant interaction is observed across time period (Chi-Square (4 d.f.)=1.78, p=.78).

While clearly no significant relationship exists between exposure and number of children with abnormalities and early childhood ilnesses, the relationship between exposure and miscarriage-stillbirth is less clear. The previous analyses do not consider one of the strongest predictors of miscarriage. With each miscarriage the risk that future pregnancies will result in a miscarriage is increased.

TABLE 7-11: Pregnancies Classified by Number of Prior Miscarriages and Outcome and Exposure.

Group	Outcome	Number of Prior Miscarriages				Total
		None	One	Two	Three or More	
Exposed	Miscarriage	64	19	6	7	96
	Live birth	554	19	2	4	579
	Total	618	38	8	11	675
Non-Exposed	Miscarriage	50	11	3	2	66
	Live birth	603	16	0	2	621
	Total	653	27	3	4	687

Chi-Square MH(1d.f.)=3.15, p=.076.
Interaction Effect: Chi-Square(3d.f.)=.65, p=.89.

Table 7-11 tabulates pregnancy outcomes by exposure group status and number of prior miscarriages. The relationship between exposure group status and miscarriage rate is marginally significant (Chi-Square MH (1 d.f.)=3.15, p=.076) and it does not vary across number of prior miscarriages (Chi-Square (3 d.f.)=.65, p=.89). Regardless of the number of previous miscarriages, the exposed group's pregnancies tend to have a higher miscarriage rate than the non-exposed.

However, when examining that same relationship for the exposed group only (Table 7-12), the relationship between pregnancy outcome and exposure in terms of father's work history is not significant (Chi-Square MH (1 d.f.)=.74, p=.39).

TABLE 7-12: Pregnancies of Exposed Group Classified by Number of Prior Miscarriages and Outcome and Exposure Status.

Exposure Status	Outcome	Number of Prior Miscarriages				Total
		None	One	Two	Three or More	
Pre-Exposure	Miscarriage	37	9	2	4	52
	Live birth	384	4	0	2	390
	Total	421	13	2	6	442
Exposure and Post-Exposure	Miscarriage	27	10	4	3	44
	Live birth	170	15	2	2	189
	Total	197	25	6	5	233

Chi-Square MH (1d.f.)=.74, p=.39
Interaction Effect: Chi-Square (3d.f.)=5.57, p=.13

While the miscarriage rate is lower for pregnancies prior to time of exposure than for pregnancies that took place during and after exposure, conditional on no prior miscarriages, the rate with one, two and three or more prior miscarriages tends to be higher for pregnancies that took place prior to time of exposure. Overall, no significant interaction is observed across number of previous miscarriages (Chi-Square (3d.f.)=5.57, p=.13).

Adjusted comparison: miscarriage-stillbirth outcome. In this final analysis only pregnancy outcome (live birth or miscarriage-stillbirth) of the exposed group is analyzed. Pregnancy outcome remains the unit of analysis. This analysis will be limited to 668 pregnancies for which complete data exist on all variables of interest: Mother's age at time of conception, mother's smoking and drinking history, exposure level at time of conception, and pregnancy history. Father's age at time of conception has been omitted because of its high correlation with mother's age.

Logistic regression models can be used to estimate the probability that a pregnancy results in a miscarriage-stillbirth.

TABLE 7-13: Predictors of a Miscarriage-Stillbirth Outcome. Logistic Regression Analysis (N=668)

	MODEL I		MODEL II		MODEL III	
Predictors	COEF[1] (SE)	Estimated Odds Ratio	COEF (SE)	Estimated Odds Ratio	COEF (SE)	Estimated Odds Ratio
Mother's Age	.020 (.021)	1.02	.021 (.020)	1.02	.032 (.019)	1.03
Mother Smoking: yes vs. no	.118 (.252)	1.13	.130 (.252)	1.14	.437 (.232)	1.55
Mother Drinking: yes vs. no	-.028 (.387)	.97	.016 (.361)	1.02	-.030 (.331)	.97
Exposure: HGPEAK (Year of Conception)	.0005 (.0005)	1.00			.0005 (.0005)	1.00
Previous Miscarriages	1.28* (.215)	3.60	1.29* (.216)	3.63		
-2 Log (Likelihood)	488.81		489.58		538.47	
(Degree of freedom)	(5)		(4)		(4)	
Significance for Equation	p = .0001		p = .0001		p = .09	

[1] Coefficient and its standard error. * indicates $p < .05$.

Many of the commonly cited predictors of a miscarriage-stillbirth outcome such as mother's smoking and drinking history or mother's age at time of conception are not powerful predictors in our sample population (Table 7-13, model I). The strongest predictor is the number of previous miscarriages ($p < .0001$). The estimated odds ratios for the possible confounders remain consistent whether exposure is in the model (model I) or not (model II). HGPEAK, the peak mercury level for the year of conception,

is the exposure measure used in this analysis. Regardless of exposure measure - HGPEAK (year of conception), HGPEAK (lifetime, prior to and including year of conception), HGU-LEQU (year of conception), HGU-LEQU (lifetime prior to and including year of conception) - the estimated odds ratio for exposure remains non-significant (estimated odds ratio = 1.00). Comparing the -2 Log Likelihood of models I and II shows that pregnancy outcome and exposure level at time of conception are not significantly related. However, comparison of the -2 Log Likelihood of models I and III shows that number of previous miscarriages and birth outcome are not independent of each other ($p<.001$). There is no significant interaction of exposure and number of previous miscarriages (not shown).

Logistic regression analysis which includes both exposure level and number of previous miscarriages suggests that it is wife's prior history of having miscarriages and not husband's exposure level that is the significant predictor of the probability that a pregnancy results in a miscarriage. Furthermore, the correlation of the parameter estimates for exposure and number of previous miscarriages in this logistic model (model I) is very weak ($r=-.02$). This analysis supports the observation that while the two groups (exposed and non-exposed) probably differ in miscarriage rates, the timing of exposure is not a significant predictor of miscarriages among the exposed group.

Summary

For several of the pregnancy outcome variables we found no relationship between exposure and the reproductive outcome. There was no evidence of a reduction in fertility or higher rate of abnormalities or illnesses in the children of the exposed workers. However the relationship between exposure and one measure of outcome - the rate of miscarriage-stillbirth -

was more complex. Several approaches have been used to gain a better understanding of the relationship between exposure and selected pregnancy outcomes in general and rate of miscarriage-stillbirth in particular. In the simple, unadjusted group comparison (table 7-3) the mean difference in miscarriage-stillbirth outcome between the exposed and the non-exposed groups approached statistical significance ($p<.10$), with the exposed group having more miscarriages-stillbirths per subject than the non-exposed. The differences remained at least marginally significant when adjusting for possible confounders (Table 7-5). A more sensitive dose-response analysis, adjusting for selected confounders, revealed that the cumulative mercury measure (HGU-LEQU) correlated significantly with miscarriage-stillbirth outcome (Table 7-6 and 7-7). This analysis has two weaknesses. It does not consider either the temporal relationship between exposure and miscarriages nor the role of a mother's previous miscarriage on the risk of future miscarriages.

Treating pregnancy outcome as unit of analysis, unadjusted comparison by exposure group and plant exposure history (Table 7-8) yielded an overall significant relationship between exposure group membership and miscarriage-stillbirth outcome. That same relationship was marginally significant when the outcomes were grouped by number of prior miscarriages (Table 7-11), but it was non-significant when examining the impact of exposure on pregnancy outcome for the exposed group only (Table 7-12).

When adjusting for personal characteristics such as mother's age at time of conception, mother's smoking and drinking history, and mother's number of previous miscarriages, exposure level at time of conception was not a statistically significant predictor of the probability of having a

miscarriage (Table 7-13). The strongest predictor of a miscarriage-stillbirth outcome appeared to be number of previous miscarriages.

In conclusion, the data collected on the Y-12 workers do not clearly suggest that exposure is related to a miscarriage-stillbirth pregnancy outcome. Rather, it appears that the propensity to have a miscarriage (number of previous miscarriages) is a strong predictor of a miscarriage-stillbirth outcome and that such propensity is probably not related to exposure to mercury.

8. ASSESSMENT OF RENAL FUNCTION

Background

Mercury may cause damage to the kidney if it is able to accumulate in sufficient amounts. The quantification of protein enzymes that originate in the kidney and are excreted in the urine has been useful in identifying subtle evidence of renal dysfunction due to heavy metals and other renal diseases and toxins (Buchet 1980, Foa 1976, Roels 1978, Roels 1985).

The principal measure of renal effect in this study was level of N-acetyl-B-glucosaminidase activity in the urine of exposed and non-exposed subjects. N-acetyl-B-glucosaminidase has been shown in previous studies (Buchet 1980, Foa 1976, Meyer 1984) to be a sensitive indicator of early renal damage. In the above study the authors suggested that exposure to elemental mercury may be associated with a slight glomerular dysfunction. Total protein and albumin were included because these measures have been observed to be sensitive to other heavy metals such as cadmium (Falck 1983).

In addition to being a sensitive indicator, N-acetyl-B-glucosaminidase meets other criteria for urinary enzyme analysis those being it is stable when frozen and thawed and methods for detection are well known, (Leaback 1961) and semiautomated.

Results

Subjects. All but two of the 502 subjects examined gave urinary samples of sufficient volume for laboratory analysis. Adjustment per gram of creatinine limited the analyses to the 499 subjects who had a creatinine measurement. The enzyme test was reported on samples from 484 of these 499 subjects.

Group comparison. In the overall group comparison presented in chapter 4, there were no statistically significant differences between the mercury-

exposed group and the control group on any of these measures before adjustment for age or other potentially important factors. Likewise, the comparison of these same two groups when adjusting for both age and lead exposure did not give any statistically significant differences. In a more detailed group comparison, after using stepwise forward regression to identify covariates that had a significant influence upon these measures, (Table 8-1) adjusting for age, reported lead exposure, reported hypertension, and recorded diabetes, none of these three urinary measures gave a statistically significant differences between the mercury-exposed group and the control group.

TABLE 8-1: ADJUSTED GROUP COMPARISON: Urinary Results

Response	Mercury N = 246 Mean	Control N = 254 Mean	Covariance a. signif
Protein (mg/gm Cre)	78.3	75.4	.45
Albumin (mg/gm Cre)	22.4	24.8	.27
BNAG (umole/gm Cre)	1.94	1.47	.21

* $p<.05$, ** $p<.01$
a. Adjusting for age, hypertension, diabetes, and lead exposure.

Dose-response analysis. The following regression analyses were performed on all subjects (N=500) without making any exclusions. The positive coefficients for the three urinary outcome measures indicate that the mean level of these measures increased as the urine mercury history variable increased. This was true for both the integrated measure of exposure and the peak measure of exposure. The heavy weight protein of interest, N-acetyl-B-glucosaminidase, is significantly ($p<0.05$) associated with both of the urine mercury history variables included in these regression analyses. These regression models control for the contribution of age, lead exposure,

reported hypertension, and recorded diabetes upon each of these outcome measures.

TABLE 8-2: DOSE-RESPONSE ANALYSIS: Urinary Results (Cases=All)

Variable	HGU Regression (N=500) Partial Corr	p-value	HGPEAK Regression (N=500) Partial Corr	p-value
Protein (mg/gm Cre)	.049	.27	.063	.16
Albumin (mg/gm Cre)	.067	.14	.035	.44
BNAG (umole/gm Cre)	.110	.02*	.095	.04*

* $p<.05$, ** $p<.01$
Cre: Creatinine

There was the possibility that a small number of individual subjects were responsible for the statistically significant regression coefficients found between the urine mercury history variables and the level of N-acetyl-B-glucosaminidase. Visual analysis of bivariate scatter plots of these two significant relations was conducted to identify individuals with the highest level. The five subjects with the highest BNAG values were identified from each of these plots. The regressions were performed again without these cases. For the integrated urine history mercury variable the relation was significant ($p<.02$), indicating that the overall regression equation was not greatly influenced by a small number of points (N=5). For the peak urine history mercury variable the regression was not significant ($p<.09$), indicating that the overall regression equation was influenced by a small number of points (N=5).

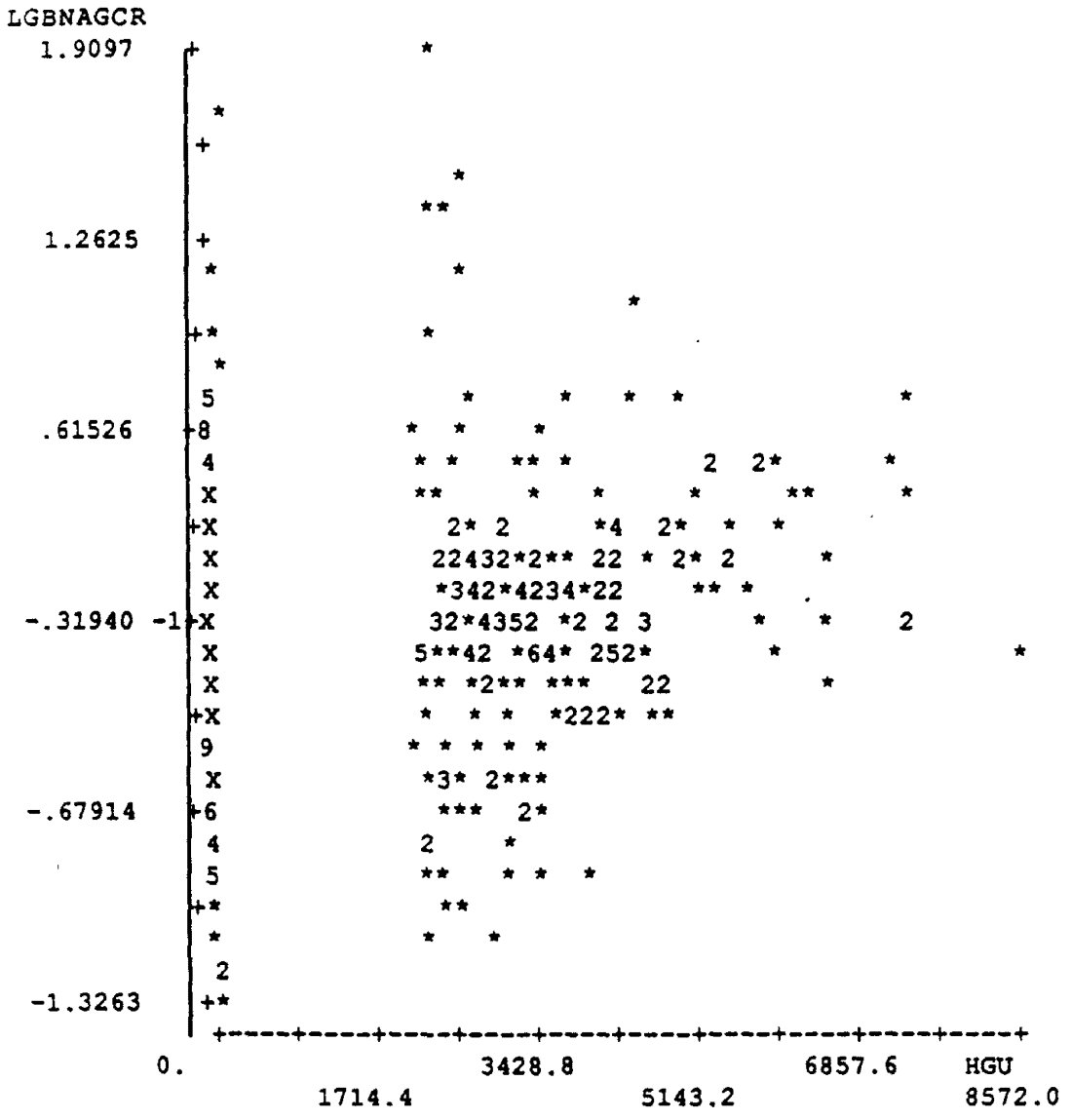


Figure 8-1: Scatter Plot of Log N-acetyl-B-glucosaminidase/gram of Creatinine Vs. Cumulative Urine Mercury (HGU)

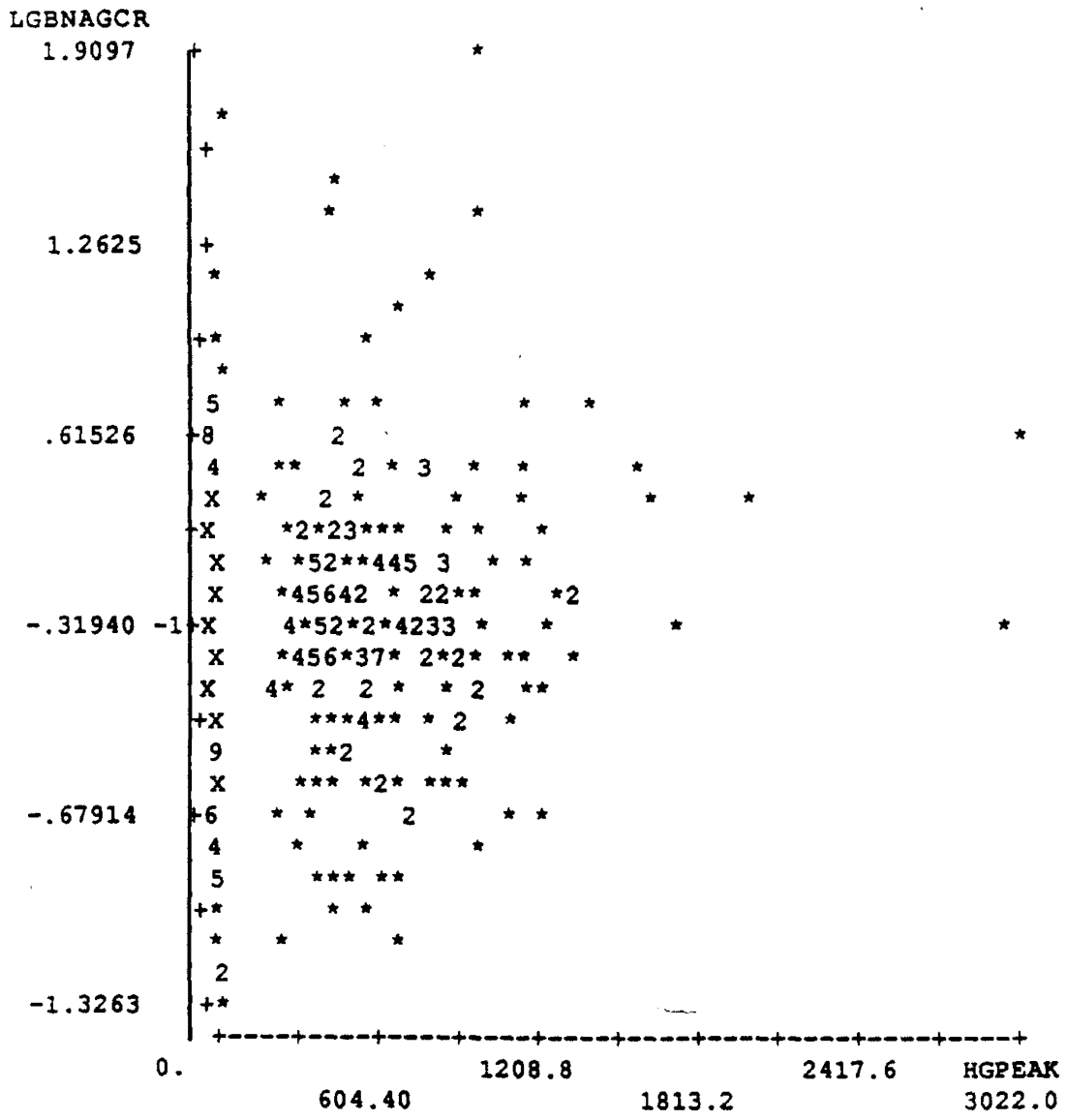


Figure 8-2: Scatter Plot of Log N-acetyl-B-glucosaminidase/gram of Creatinine Vs. Peak Urine Mercury (HGPEAK)

Selective Evaluation of Subjects with High Mercury Exposure

The positive regression coefficients described above suggest a possible dose-response relation between the urine mercury history variables and the current urinary measures. To examine the nature of this suggested dose-response relation, the group of study subjects was divided into two groups: those who had one or more urine mercury peaks above 0.6 mg/L (n=111) and those without a history of such peaks (n=389). A significant difference ($p < 0.5$) existed in the mean level of N-acetyl-B-glucosaminidase with the higher level occurring in those subjects with one or more urine mercury peaks above 0.6 mg/L.

TABLE 8-3: GROUP COMPARISON: Subjects with One or More Urine Mercury Peaks > 0.6 mg/L to Subjects without Such Peaks

Response	Urine Mercury Peak > 0.6 mg/L		
	Yes N=111	No N=389	Covariance a. signif.
Protein (mg/gm Cre)	86.1	74.2	.09
Albumin (mg/gm Cre)	22.8	23.8	.28
BNAG (umole/gm Cre)	2.4	1.5	.05*

* p<.05, ** p<.01
a. Adjusting for age, hypertension, diabetes, and lead exposure.

The most significant covariate in these analyses has been age. The increased level of N-acetyl-B-glucosaminidase found in the mercury exposed group may be expressed in terms of age in years rather than as integrated mercury exposure (ug/L). Thus, an exposure to 3,200 ug/L integrated urine mercury is roughly equivalent to the effect on N-acetyl-B-glucosaminidase level as ten years of aging. In terms of the peak urine history variable, a peak exposure of 770 ug/L is roughly equivalent to the effect on N-acetyl-b-glucosaminidase level as ten years of aging.

Clinical Relevance of Renal Measures

For each of the renal measures a clinically abnormal level was defined as a level which was three standard deviations above the mean of the comparison gorup (protein > 56 mg/gm Cre., albumin > 383 mg/gm Cre., and BNAG > 7.56 umole/gm Cre.). The standard deviations were based on the comparison group. Two percent (5) of the exposed subjects had an abnormal level of protein while one percent (3) of non-exposed subjects had an abnormal level (Fisher's Exact Test, p = .35). One percent of both the exposed and non-exposed subjects had an abnormal level of albumin. Two percent (5) of the exposed subjects had an abnormal level of BNAG while one percent (2) of non-exposed subjects had an abnormal level (Fisher's Exact Test, p = .21). All of the individuals with elevated protein or albumin in their urine had either several risk factors for renal disease such as hypertension, diabetes, and extensive cardiovascular disease or a history of renal disease. Despite the relationship between mercury exposure and BNAG, there was no evidence of clinically meaningful renal dysfunction or disease in the exposed group when compared to the non-exposed group.

Discussion

The renal function of the subjects was not as extensively evaluated as the functioning of the peripheral and central nervous system. The simple comparisons between the exposed and non-exposed subjects revealed no differences in the measures of renal functioning. There was evidence of significant but weak relationships between the amount of N-acetyl-B-glucosaminidase (BNAG) and integrated or peak measure of exposure to mercury. The statistical significance of this relationship was not dependent on a few individuals for the integrated exposure but was dependent on a few individuals for the peak exposure relationship. These relationships were significant after adjustment for hypertension, diabetes,

age and lead exposure. Neither albumin or protein were related to the level of intensity of exposure. BNAG was also related to exposures above a peak urine value of 0.6 mg/L after adjustment for age, hypertension, diabetes, age, and lead exposure. The rate of abnormal levels of urinary protein and albumin was not different in the mercury exposed and non-exposed groups. The relationship between mercury and BNAG did not appear to have any clinical importance.

9. Quantitative Measures of Lead Exposure and Uranium Exposure.

Lead Exposure

Lead is a neurotoxin and could have a significant effect on the outcome of many of the measures studied in this investigation. Unlike inorganic mercury, lead may accumulate in the body over extended periods of time.

All workers exposed to lead at Y-12 were enrolled in a biological monitoring program. The measure of lead exposure developed for the following analyses was based on each workers cumulative urinary lead exposure during this time period taken as the sum of each worker's yearly average exposure level for lead.

Urinary lead is a good indicator of the current absorption of lead, but is a less precise measure of exposure than blood lead. A level of 0.20 mg/L of lead in urine has been associated with a level of about 0.08 mg/100ml of lead in blood. After applying a correction for the specific gravity of urine (1.016) this would give a corresponding level of about 0.15 mg/L for an acceptable limit of lead in urine. In the 16 year period that urinalyses for lead were conducted at Y-12 there were only 2 individual readings on this group of workers that exceeded this level.

Total lead exposure and average lead exposure over this period of time at Y-12 did not show a statistically significant difference between the group of workers exposed to mercury and those workers not exposed to mercury. However, there was a statistically significant greater number of workers in the mercury exposed group than in the group of workers not exposed to mercury that were also exposed to lead at Y-12 (15.8% vs. 5.1%; chi-square = 15.4, $p < 0.0005$).

When the outcome measures significant for mercury exposure were re-examined including a term for cumulative exposure to lead at Y-12, none of the outcomes examined showed a significant association with exposure to lead. This may be explained by the combination of relatively low levels of exposure to lead and the small number of individual workers with such exposure.

TABLE 9-1: Analysis of Outcomes Significant for Mercury: Significance of Quantitative Measure for Cumulative Lead Exposure.

Variable	Total Urinary Lead Partial Corr	p-value
MOTOR EXAMINATION		
Strength:		
Proximal Strength	0.01	0.82
Distal Strength	0.02	0.73
Tremor:		
Sustention Tremor	0.007	.88
Acc Tremor RMS (mm/s*2)	-0.02	.71
Acc Tremor Ave Amplitude	-0.02	.65
SENSORY EXAMINATION		
2-pt. Discrimination		
hand:	-0.07	.12
foot:	-0.03	.50
Touch Sensation		
foot:	-0.01	.81
Vibration		
foot:	0.05	.31
Psychomotor Performance (N=482)		
Onehole: Number of Pins	-0.05	.34
Hand-eye coordination (RMS)	-0.01	.86
Electrodiagnostic Evaluation (N=383)		
# Sn. Nerves Abnormal	-0.01	.87
# Mt. Nerves Abnormal	-0.06	.28
Urinary measure (N=502)		
log BNAG	0.02	.59

* p<.05, ** p<.01
Adjusting for age (years), height (inches), weight (lbs), and known clinical abnormality categories (no,yes).

Similarly, when the outcome measures significant for mercury exposure were re-examined including a term for cumulative exposure to uranium at Y-12, based on each worker's equivalent lung absorbed dose (mrem), none of the outcomes examined showed a significant association with exposure to uranium. The neurologist's rating of tremor (sustension tremor) was marginally significant (p=.06).

TABLE 9-2: Analysis of Outcomes Significant for Mercury: Significance of Quantitative Measure for Cumulative Uranium Exposure.

Variable	Total Lung Equiv. Uranium Partial Corr	p-value
MOTOR EXAMINATION		
Strength:		
Proximal Strength	-0.01	.76
Distal Strength	-0.06	.20
Tremor:		
Sustention Tremor	0.08	.06
Acc Tremor RMS (mm/s*2)	0.04	.36
Acc Tremor Ave Amplitude	0.06	.22
SENSORY EXAMINATION		
2-pt. Discrimination		
hand:	0.06	.18
foot:	0.07	.12
Touch Sensation		
foot:	0.07	.15
Vibration		
foot:	-0.007	.87
Psychomotor Performance (N=482)		
Onehole: Number of Pins	0.05	.33
Hand-eye coordination (RMS)	-0.04	.40
Electrodiagnostic Evaluation (N=383)		
# Sn. Nerves Abnormal	-0.08	.13
# Mt. Nerves Abnormal	-0.07	.16
Urinary measure (N=502)		
log BNAG	0.05	.30

* p<.05, ** p<.01
Adjusting for age (years), height (inches), weight (lbs), and known clinical abnormality categories (no,yes).

10. SUMMARY

Introduction

In this summary, we will review briefly the results from the four major parts of the report: (1) clinical, quantitative neurologic examination, and electrodiagnostic evaluation; (2) tremor and behavioral tests; (3) reproductive health; and (4) renal (kidney) assessment.

Generally, in each section, first the comparison between the mercury and non-mercury exposed subjects will be discussed. Covariance analysis was used in the simple comparison analysis to adjust for differences in age, diabetes, hypertension, use of alcohol and lead exposure if these covariates were significantly related to health outcome measures. After the simple comparison analyses either multiple regression analysis or multiple logistic regression was employed to determine if there was a relationship between total amount (cumulative) or intensity of the mercury exposure and the health outcome variables. When statistically significant differences were observed between the exposed and non-exposed groups, the clinical importance of the differences are briefly discussed.

Clinical and Electrodiagnostic Evaluation

The simple comparisons of the clinical, quantitative neurologic examination and electrodiagnostic evaluation demonstrated after adjustment for covariates only two significant differences between mercury exposed and comparison groups. Both of these differences (decreased proximal strength and sensory median amplitude) were small in magnitude and had no clinical meaning. In the dose response analyses eleven of the approximately sixty clinical, quantitative and electrodiagnostic variables were weakly and significantly related to either integrated (cumulative) or peak urine mercury exposure. Several of these relationships were dependent on a small number of subjects (no more than 3). However, all of the eleven demon-

strated poorer function or more abnormalities in the mercury exposed group. The dose response studies were insufficient to conclude that prior mercury exposure was associated with a chronic sensorimotor peripheral polyneuropathy. Many of the key signs of sensorimotor polyneuropathy such as prolonged distal latency of median, sural, or ulnar nerves or diminished muscle stretch reflexes were not related to mercury exposure. The overall pattern of the eleven clinical, quantitative, and electrodiagnostic variables was not consistent with any single central or peripheral nervous system disorder.

Subjects with urine mercury peak levels above 0.6 mg/L demonstrated significantly, slightly poorer performance than remaining subjects, including decreased strength, decreased coordination, increased tremor, decreased sensation, and increased prevalence of Babinski and snout reflexes, consistent with small, subclinical central and peripheral nervous system adverse effects. Although exposure was not age-dependent, several neurologic measures showed significant age-mercury interaction suggesting that natural neuronal attrition may unmask prior subclinical abnormalities.

At the end of the clinical and quantitative neurologic examination each neurologist assessed whether the subject had a polyneuropathy based on the results of the clinical and quantitative examination. The percentage of subjects with polyneuropathy in the exposed and non-exposed groups were similar. However, when we examined the fifty one subjects with peak exposures above .850 mg/L, twenty seven percent of the subjects had a clinical diagnosis of polyneuropathy compared to ten percent of all the other subjects including those with no exposure and with lower exposure. A multiple logistic regression analysis suggested that this excess number of subjects with a clinical diagnosis of mild polyneuropathy in the highest

exposure group persisted after adjustment for the potential confounding factors of age, diabetes, lead exposure, use of alcohol and other co-existing illnesses. Subjects with exposures above .850 mg/L appear to have about a two to three fold increased risk of a mild clinical polyneuropathy compared to subjects with either no exposure or lower exposures. Only fifty one subjects had exposures which exceeded .850 mg/L.

Two reasons explain why the dose response analysis of individual clinical, quantitative, and electrodiagnostic health outcomes do not as strongly support the relationship between polyneuropathy and high peak exposure to mercury. First, the number of excessive cases is small (about five cases). Second, the cases of polyneuropathy were mild. One surprising observation is that motor nerve abnormalities appear to be more strongly related to mercury than the sensory nerve abnormalities. In our past studies we observed the opposite relationship between the motor and sensory nerve abnormalities.

Results of Tremor and Behavioral Tests

Tremor Results

The results of this section will be presented in three parts: (1) quantitative measure and neurologist's rating of sustention forearm tremor; (2) psychomotor tests - reaction time, one hole test, and hand-eye test; and (3) cognitive tests - symbol digit test, vocabulary, and mood. The tremor was analyzed quantitatively in two ways. The first is measurement of the displacement of the tremor and the second is measurement of the acceleration of the tremor. The second method is considered more sensitive to the effects of mercury. In our data the most significant results were observed with the acceleration of the tremor. In the simple comparison of the exposed to non-exposed subjects, none of the measures of the acceleration of the tremor were significant. When we compared the subjects

with no urine mercury peaks greater than 0.6 mg/L to the subjects with one or more urine peaks greater than 0.6 mg/L, several measures of the acceleration of the tremor were significantly different in the higher exposure group. Our initial hypotheses were that the exposed subjects would have a higher root mean square amplitude and a lower frequency of the neuromuscular peak component of the tremor. The higher exposed subjects (one or more urine peaks > 0.6 mg/L) had a significantly higher amplitude but did not have a lower frequency of the neuromuscular peak. In the dose response analysis there was a weak significant relationship between the magnitude of the urine peak exposure and the acceleration tremor amplitude, however the significant relationship was dependent on results from a few subjects.

Analysis of the neurologist's rating of tremor suggested a relationship between the number of urine peaks > 0.6 mg/L and presence of tremor. Based on the neurologist's ratings it is possible that approximately five of the most heavily exposed workers (urine mercury peak > .6 mg/L) may have mild residual tremor. In the entire group of the highest exposed workers only three had a moderate tremor. For the vast majority of subjects regardless of exposure level there is no evidence of a definite tremor.

Psychomotor Results

In the simple comparisons of the exposed group with the non-exposed group, the reaction time and one hole test demonstrate no significant differences. The performance of the exposed group was slightly poorer in these two tests. In the hand-eye test the performance of the exposed group was significantly poorer. In the dose response relationships reaction time was not related to integrated or peak exposure. Performance in the one

hole test was significantly related to several measures of exposure but the strongest relationship was for the simple no-yes exposure classification. This is not strong evidence of a dose response relationship. A weak significant relationship was observed between the one hole test and some measures of exposure. This relationship was not dependent on the results of a few subjects. The psychomotor test results, overall, suggest that the exposed workers performed slightly poorer than did the non-exposed workers. Overall there was some evidence of a clear trend of worse performance with higher exposure. The small decrements found in the psychomotor tests would not be detectable in an ordinary clinical examination and most likely do not cause clinical impairment.

Although recent studies have found relationships between current mercury exposure and some measures of cognitive functioning, in our study there were no differences in cognitive functioning in the exposed subjects when they were compared to the non-exposed workers. There was no evidence of a dose response relationship between any of the cognitive measures and any of the exposure measures.

Reproductive Results

For several of the pregnancy outcomes we found no relationship between mercury exposure and reproductive outcome. There was no evidence of a reduction in the fertility or an elevated rate of health abnormalities or illnesses in the children of the exposed workers. However, the relationship between the rate of miscarriages and exposure to mercury was complex. There was a statistically significant weak relationship between integrated or cumulative mercury exposure and the rate of miscarriages. This relationship did not consider the temporal relationship between exposure and miscarriages. When we adjusted for personal characteristics known to be associated with the rate of miscarriages and the temporal

relationship of exposure to miscarriages, exposure was not a statistically significant predictor or subsequent miscarriages. All of the reproductive information is based on the recall of the subjects more than twenty to forty years after the reproductive events occurred. This suggests that compared to most of the other information collected during this study the history of reproductive events is the least reliable.

Analyses, completed since the preliminary report (which are based on cumulative exposure at the time of conception,) suggest that the maternal history of prior miscarriages and not husband's exposure level is the significant predictor of the risk of miscarriages. In conclusion, we do not believe that mercury exposure at Y-12 caused adverse reproductive outcomes.

Renal Assessment

The renal function of the subjects was not as extensively evaluated as the functioning of the peripheral and central nervous system. The simple comparisons between the exposed and non-exposed subjects revealed no differences in the measures of renal functioning. With dose response analysis there was evidence of significant weak relationships between the amount of N-acetyl-B-glucosaminidase (BNAG) and integrated and peak measure of exposure to mercury. The statistical significance of this relationship was not dependent on a few individuals for the integrated exposure but was dependent on a few individuals for the peak exposure relationship. These relationships were significant after adjustment for hypertension, diabetes, age and lead exposure. Neither albumin or protein were related to the level or intensity of exposure. The rate of abnormal levels of urinary protein and albumin was not different in the mercury exposed and non-exposed groups. The relationship between mercury and BNAG did not appear

to have any clinical importance.

Conclusion

These results should be reviewed with consideration of several factors.

(1) One should consider how biologically plausible and how consistent with past studies are these results.

(2) They must be considered in view of the strengths and weaknesses of this study. The strengths of this study include the large size of the study population, the use of multiple sensitive measurements of nervous system functioning, and a quantitative measure of mercury exposure based on individual histories. This combination of factors allows us to detect very small differences in the nervous system functioning between the exposed and non-exposed groups.

1. Sources of Bias

A. Selection Bias

A potential source of bias exists in all epidemiologic studies based upon the relative participation rates of the groups under comparison. In this study 247 out of 290 (85.2%) workers contacted in the exposed group and 255 out of 326 (78.2%) workers in the comparison group were examined. Since this was a statistically significant greater participation rate in the exposed group (chi-square = 4.91), a follow-up interview to ascertain a general description of the group that did not undergo examination was conducted by telephone. 80 interviews were conducted in this process, 52 (72.2%) in the comparison group and 28 (71.8%) in the mercury exposed group were completed. There were no important differences between the exposed workers that did and did not participate and there were no important differences between the non-exposed workers that did and did not

participate. This suggests that exposed workers who were ill were not more highly motivated than healthy workers who were exposed to participate in this study. However, there was a significant difference between those workers examined and those that were not examined in age, where the examined group averaged about three years younger (64 vs 67). This, though, would have a comparable effect upon both the exposed and non-exposed groups examined and would not bias the results of this study.

Another potential weakness is the possibility that the differences in the exposed and non-exposed group were related to the selection process by which subjects were originally chosen for mercury exposed jobs or by which subjects decided to be involved in this study. This type of selection process is always a theoretical possibility, however, in terms of educational level, age, and functioning on the memory, mood and vocabulary tests there were no differences between the two groups.

B. Observation Bias

All measurements of performance and assessment of health were made without the examiners being aware of the subject's exposure status. In addition some of the measures (electrodiagnostic and urinalysis) were completely objective measures not influenced by the subject's motivation or the examiners knowledge. Overall, the level of cooperation and motivation that we received from the subjects was excellent.

C. Confounding

The major sources of confounding were most likely identified prior to examination. Age and educational status were matched in the selection of the comparison group and neurotoxic exposures (alcohol, medications, and other occupational exposures) were adjusted for in the analyses. Non-occupational diseases (diabetes and hypertension) were also considered in the analyses. A quantitative measure of lead exposure from each worker's

Y-12 records was also adjusted for in the analyses. The quality of the data collected on such factors as alcohol use and health status may be limited as it was based on a medical history or obtained by questionnaire.

D. Misclassification

Random misclassification of exposure or disease would tend to reduce the strength of an association between exposure and health outcome. While many of the non-exposed workers reported some degree of mercury exposure on the questionnaire, after 1955 we believe participation in the urine screening program is a reasonable measure of exposure. Analyses underway will allow us to estimate the extent of mercury exposure among workers who reported exposure but who never had a positive urine for mercury based on employment histories.

2. Assessment of Causality

A. Specific to a study

i) strength of association

In past studies the strength of the association between mild tremor and mild polyneuropathy and mercury exposure were generally stronger. However, these studies were of workers with current or more recent exposure to mercury.

ii) dose-response

Our best indication of an association between tremor and polyneuropathy and mercury exposure was the evidence provided from linear regression models and the group comparison of more highly exposed to those with lower exposure. Both of these findings were consistent with a dose-response relationship indicating poorer performance on a number of measures (including tremor and polyneuropathy) with increasing exposure to mercury. A small number of subjects with the highest exposure had a mild

polyneuropathy probably related to their mercury exposure.

iii) specificity of risk to disease subgroup

The oldest workers (over 70 years) with intense exposure had the poorest performance, while intensely exposed younger workers did not differ from non-exposed workers of a similar age.

iv) specificity of disease to exposure subgroup

Many of the measures examined indicate decreasing performance but not necessarily of impairment. Though, most of these measures lack on an individual basis an endpoint that is clinically interpretable, this study showed a consistent pattern on both the neurological and psychomotor tests of slightly poorer performance with increased level of exposure to mercury.

v) lack of alternate explanations

We could not find convincing alternate explanations for our results. The absence of differences in the cognitive tests suggests that the two groups were similar in their rate of non-occupational serious disorders of the central nervous system.

B. External to a study

i) results of other studies

The possible associations between mercury exposure and mild tremor, mild polyneuropathy, and elevated N-acetyl-B-glucosaminidase levels observed in this study all have been observed in some past studies on occupational exposure to elemental mercury as discussed in their respective chapters. A difference between the findings of this study and our previous work is the observation that the relationship between a history of higher mercury exposure and specific abnormality is stronger for electrodiagnostic motor nerve compared to sensory nerve abnormalities.

ii) biologic plausibility

The slightly poorer performance of exposed workers on some of the

quantitative neurological and psychomotor measures is more difficult to evaluate with regard to biologic plausibility and consistency with past studies. The poorer performance is not clearly related to dysfunction of a specific part of the central or peripheral nervous system. A possible explanation is that intense exposure to mercury caused a small amount of subclinical damage to several different parts of the nervous system. The effect of this damage is most apparent in the oldest workers because of unmasking effects due to the normal ageing process.

Whether these small differences in performance caused impairment in the past or today, is impossible to determine within the scope of this research project. This study did not ascertain the health of these workers immediately following exposure and it is possible that some of these workers were adversely affected in the past, related to their mercury exposure. The current health of the majority of workers who were exposed to mercury has not been adversely affected. A small number of the most heavily exposed workers have mild clinical conditions (polyneuropathy or tremor) probably related to their mercury exposures. Follow-up surveillance of the most heavily exposed workers is warranted on the basis of the results of this study. Details regarding this recommended surveillance will be provided in an additional report when we have reviewed any further critiques of this final report and completed our remaining analyses.

Appendix 1.

Job Titles Used in Matching Controls to Exposed

Listing of Job Titles Used In Matching

0 = omit

GUARD

1 = unskilled labor

CLEANER
CLEANR LAB EQUIP
HELPER
JANITOR
LABORER

2 = semi-skilled labor

ASSEMBLER
ASSEMBLY MAN
ASST OPERATOR
ASST RECREATION
ASST SERV OPER
ATTENDANT COUNT
CASHIER
CHAUFFEUR
CHEMICAL OPER
DISPATCHER ELEC
DISPATCHER MAT
DRIVER EQUIPMEN
DRIVER TRUCK
FOUNDRYMAN
HAND MACHINE
HANDLER MATERIA
HANDLER SALVAGE
INSP PROD FAB
INSPEC PROD FAB
INSPEC RADIATIO
INSPECT PROD FAB
INSPECTOR
INSPECTOR FIRE
INSPECTOR MATR
INSPECTOR SHOP
KEEPER SALV YARD
KEEPER SALV YD
KEEPER SALVAGE
KEEPER YARD
MACH PROD FAB
MACHIN PROD FAB
MACHINE SET UP
MAN MATERIALS
MAN PARTS
METAL FABRICATOR
OPER ASST SERV

OPER CHEM PROC
OPER FIRETRUCK
OPER MACHINE
OPER PROC SERV
OPER STEAM PLANT
OPER STEAM PLT
OPERATOR
OPERATOR ASST
OPERATOR CHEM
OPERATOR CHEMI
OPERATOR CHEMIC
OPERATOR CRANE
OPERATOR EQUIP
OPERATOR EVAPOR
OPERATOR LAUNDR
OPERATOR MACH
OPERATOR MACHI
OPERATOR MACHIN
OPERATOR PILOT
OPERATOR PROC
OPERATOR PROCES
OPERATOR PROD
OPERATOR RECOVE
OPERATOR SALVAG
OPERATOR SERVIC
OPRATR CHEM PROC
PAINTER
PROCESS OPER
STOCK KEEPER
WASHER WINDOW
WORKER METAL

3 = skilled labor

ASST SKILL TRA
ASST STEAM PLANT
BAKER
BOILERMAKER
CARPENTER
DRAFTSMAN
ELECTRICIAN
ELECTROPLATER
EMP MAINT SERV
FABRICATOR
FINISHER CEMENT
HEAT TREATER
HELPR SKIL TRA
INSPEC HLTH PHYS
INSTRUMENT MECH
INSULATOR
IRONWORKER
MACHINIST
MACHINIST FAB

MACHINIST HELPER
MACHINIST MAINT
MACHINIST PF
MACHINIST PROD
MACHINIST SET UP
MAKR MECH INSTR
MAN SHOP MAINT
MASON BRICK TILE
MECH ELEC MAINT
MECHANIC
MECHANIC DEV
MECHANIC DEVEL
MECHANIC INST
MECHANIC INSTR
MILLWRIGHT
PIPEFITTER
PROD MACHINIST
RADIOGRAPHER
RIGGER
RIGGER IRONWKR
RIGGER&IRONWKR
SPEC MACHINE
SPECIAL MACHIN
SPECIAL MACHINE
SPECIALIST
SPECIALIST MACH
TECH MEDICAL
TREATER HEAT
WELDER

4 = foreman/supervisor

ASST STEAMPLANT
FORE ASST CRAFT
FORE ASST PROC
FORE ASST PROCES
FORE REFIN RECOV
FOREMAN CRAFT
FOREMAN FOUNDRY
FOREMAN LUB
FOREMAN MACH
FOREMAN MAINT
FOREMAN PROCESS
FOREMAN UTILITY
HEAD DEV DEPT
HEAD DEV SECTION
HEAD INSP DEPT
HEAD PROC DEPT
SUPER PROC SERV
SUPERVISOR DESI

5 = white collar

AIDE ENGINEER
AIDE REPRODUCTN
ANALYST LAB
ASST REPROD
CHIEF MAIL SERVI
CLERK
CLERK ACCTN
CLERK MAIL
CLERK RECEIVING
CLERK RECORD
CONSULTANT DEV
DESIGNER
DETLR AND ESTMTR
DRAFTSMAN ENGR
EDITOR NEWS
MAIL CLERK
PLANR ESTMTR
SECRETARY
STENOGRAPHER
TECHNICIAN ENGR
TIMEKEEPER
TRAINEE LAB

6 = engineer

ASSISTANT ENGR
ASST ENGINEER
CHEMIST
ENGINEER
ENGINEER ASSO
ENGINEER ASSOC
ENGINEER DESIGN
ENGINEER DEV
ENGINEER INDUST
ENGINEER PROCES
ENGINEER PROD
ENGR ASSOC DES
ENGR ASSOC INDST
SPECIALIST ENGR

Appendix 2. (a)

Health Questionnaire Part I

HEALTH QUESTIONNAIRE PART I

The answers to these questions are confidential. Do not be concerned if you have trouble answering any of these questions. An interviewer will go over this questionnaire with you before you hand it in.

Interviewer:_____

Today's Date:___ ___/___ ___/___ ___
month day year

_____

Put label here

_____

1) Phone Number: ( ) ___ ___ ___-___ ___ ___ ___

2) Birthdate: ___ ___/___ ___/___ ___
month day year

3) What is the highest level of education that you have completed?

(circle the number of years completed)

Elementary	1 2 3 4 5 6 7 8
High School	9 10 11 12
College	13 14 15 16+

4) Where were you born? USA_____ Other_____

5) What language do you speak at home? English_____ Other_____

1) Have you **ever** been hospitalized for or has a doctor **ever** told you that you have any of the following conditions or diseases:

	YES	NO
a) Loss of consciousness from a head injury	( )	( )
b) tuberculosis	( )	( )
c) cancer, leukemia or brain tumor	( )	( )
d) epilepsy, seizures, or convulsions	( )	( )
e) anemia (low blood count)	( )	( )
f) polio	( )	( )
g) syphilis	( )	( )
h) high blood pressure	( )	( )
i) Have you received medication for high blood pressure?	( )	( )
j) kidney disease	( )	( )
k) encephalitis or meningitis	( )	( )
l) multiple sclerosis (M.S.)	( )	( )
m) Parkinson's disease	( )	( )
n) other diseases of the brain or nervous system	( )	( )
(explain)_____		
o) diabetes (sugar)	( )	( )
p) family history of diabetes (close family only)	( )	( )
if yes: i grandparents	( )	( )
ii parents	( )	( )
iii brothers/sisters	( )	( )
iv children	( )	( )
q) hand tremor	( )	( )
r) family history of hand tremor (close family only)	( )	( )
if yes: i grandparents	( )	( )
ii parents	( )	( )
iii brothers/sisters	( )	( )
iv children	( )	( )
s) surgery requirring hospitalization	( )	( )
t) serious heart problems	( )	( )
u) thyroid problems	( )	( )

	YES	NO
2) a) Are you **now** under a doctor's care?	( )	( )

b) If yes, for what condition(s):

_____

_____

_____

3) Do you take any medicine(s) regularly? YES ( ) NO ( )

If yes, please list all prescription and over-the- counter medicines that you are taking: (If you don't know the name, still give the color of the medicine and why you take it).

	Name of Medicine	Reason for Taking	Amount/Day	When Started
a)				
b)				
c)				
d)				
e)				

4) Have you **ever** had low back trouble (ache, pain or discomfort)? YES ( ) NO ( )

If **NO** Go to **Next Page**

If **Yes**,

5) a. Have you ever been hospitalized because of low back trouble? YES ( ) NO ( )

b. Have you ever had to change jobs or duties because of low back trouble? YES ( ) NO ( )

c. What is the total length of time that you have had low back trouble during the last 12 months?

( ) 0 days
( ) 1-30 days
( ) More than 30 days, but not every day
( ) Every day

d. Have you ever had low back trouble (ache, pain or discomfort) that spread into your upper or lower leg? YES ( ) NO ( )

If **yes** to d:

e. Which leg was uncomfortable? Right ( ) Left ( ) Both ( )

Below is a list of questions concerning symptoms you may have had. Check the appropriate space if you have been experiencing the symptom **IN THE PAST MONTH.**

6) a) Have you felt dizzy or lightheaded upon standing up suddenly?

__ not at all __ a little __ moderately __ quite a bit __ extremely

b) In the past month, have you felt lightheaded or dizzy otherwise?

__ not at all __ a little __ moderately __ quite a bit __ extremely

c) In the past month, have you had difficulty concentrating?

__ not at all __ a little __ moderately __ quite a bit __ extremely

d) In the past month, have you been confused or disoriented?

__ not at all __ a little __ moderately __ quite a bit __ extremely

e) In the past month, have you had trouble remembering things?

__ not at all __ a little __ moderately __ quite a bit __ extremely

f) In the past month, have your relatives noticed that you have trouble remembering things?

__ not at all __ a little __ moderately __ quite a bit __ extremely

g) In the past month, have you had to make notes to remember things?

__ not at all __ a little __ moderately __ quite a bit __ extremely

h) In the past month, have you had difficulty looking up and dialing telephone numbers?

__ not at all __ a little __ moderately __ quite a bit __ extremely

i) In the past month, have you found it hard to understand the meaning of newspapers, magazines, and books you have read?

__ not at all __ a little __ moderately __ quite a bit __ extremely

j) In the past month, have you felt irritable?

__ not at all __ a little __ moderately __ quite a bit __ extremely

k) In the past month, have you felt depressed?

__ not at all __ a little __ moderately __ quite a bit __ extremely

l) In the past month, have you had heart palpitations even when not exerting yourself?

__ not at all __ a little __ moderately __ quite a bit __ extremely

m) In the past month, have you been sleeping more often than is usual for you?

__ not at all __ a little __ moderately __ quite a bit __ extremely

n) In the past month, have you had difficulty falling asleep?

__ not at all __ a little __ moderately __ quite a bit __ extremely

o) In the past month, have you found that you wake up frequently in the early morning and cannot fall back asleep?

__ not at all __ a little __ moderately __ quite a bit __ extremely

p) In the past month, have you been bothered by clumsiness or loss of balance?

__ not at all __ a little __ moderately __ quite a bit __ extremely

q) In the past month, have you had difficulty moving your fingers or grasping things?

__ not at all __ a little __ moderately __ quite a bit __ extremely

r) Have you noticed a decrease in sweating in hot weather?

__ not at all __ a little __ moderately __ quite a bit __ extremely

7) Do you drink coffee, tea or cola beverages? YES ( ) NO ( )

If **yes**, circle best estimate of average quantities:

a) coffee	**cups/day**	0	1-3	4-6	7-9	10 or more
b) tea	**cups/day**	0	1-3	4-6	7-9	10 or more
c) cola	**glasses/day**	0	1-3	4-6	7-9	10 or more

8.) Have you **ever smoked** cigarettes regularly? YES ( ) NO ( )

If **NO** go to Question 10 (Next Page)

If YES to 8

9) a) Do you **smoke** cigarettes **now**? YES ( ) NO ( )

IF YES to 9a

b) Circle how many **cigarettes/day** you smoke **now**:

1	1-9
2	10-19
3	20-29
4	30-39
5	40 or more

c) How old were you when you first started smoking:_____(years)

d) How many years have you smoked regularly? _____ years.

e) On the **average** of the entire time you have smoked, how many **cigarettes/day** have you smoked?

1	1-9
2	10-19
3	20-29
4	30-39
5	40 or more

IF **NO** to 9a

f) If you **have quit smoking**, how old were you the last time you stopped:_____(years).

g) How many years did you smoke cigarettes regularly? _____ years.

h) On the average of the entire time you smoked, how many **cigarettes/day** did you smoke?

1	1-9
2	10-19
3	20-29
4	30-39
5	40 or more

	YES	NO
10) Have you **ever** drunk alcoholic beverages?	( )	( )

If **NO** go to Question 15 (Page After Next)

If **YES** to 10

	YES	NO
11) a. Do you **presently** drink alcoholic beverages?	( )	( )

If **NO** go to Question 13 (Top of Next Page)

If **YES** to 11a

b. How often, on average, do you drink alcoholic beverages?

( ) 6-7 days/week
( ) 3-5 days/week
( ) 1-2 days/week
( ) Less than once/week but more than once/month
( ) Less than once/month

c. When you drink, how many drinks do you average in one sitting?

( ) 1 drink ( ) 3 drinks ( ) 6-7 drinks
( ) 2 drinks ( ) 4-5 drinks ( ) 8 or more drinks

d. How long have you been drinking the above amount? _____years.

12) Give the average number of each that you drink in one week: (Leave the space blank if you don't drink that type of alcoholic beverage once/week).

___ Beer (12 oz. bottles or cans)
___ Wine (glasses)
___ Alcoholic drinks (shots of hard liquor)

---

13) a. Have you, ever in the past, been a heavier drinker than you are now? YES ( ) NO ( )

If YES: to 13a

b. How often, on average, did you drink alcoholic beverages?

( ) 6-7 days/week
( ) 3-5 days/week
( ) 1-2 days/week
( ) Less than once/week but more than once/month
( ) Less than once/month

c. When you drank, how many drinks did you average in one sitting?

( ) 1 drink ( ) 3 drinks ( ) 6-7 drinks
( ) 2 drinks ( ) 4-5 drinks ( ) 8 or more drinks

d. How long did you drink the above amount? _____years.

14) Have you **ever** in the past been told by anyone (friend, family, or doctor) that you have a drinking problem **OR** have you **ever** sought outside help related to your drinking habits (alcoholics anonymous)?

YES ( ) NO ( )

15) Please complete the following occupational history:

OCCUPATIONAL HISTORY

Please note all jobs held, starting with your present or most recent job and proceeding backwards in time since leaving school.

COMPANY	JOB TITLE	YR START	YR STOP	CHEMICALS USED

16) Have you **ever worked** with or been exposed to any of the following chemicals in a past job or in your present job?

	YES	NO	DATES(Start/Stop)
a) Uranium	( )	( )	_____
b) Thorium	( )	( )	_____
c) Cobalt	( )	( )	_____
d) X-rays	( )	( )	_____
e) Metallic mercury	( )	( )	_____
f) Lead	( )	( )	_____
g) Metallic nickel	( )	( )	_____
h) Arsenic	( )	( )	_____
i) Tellurium	( )	( )	_____
j) Berrylium	( )	( )	_____
k) Moca	( )	( )	_____
l) Perchloroethylene	( )	( )	_____
m) Trichloroethylene	( )	( )	_____
n) Carbon tetrachloride	( )	( )	_____
o) Trichloroethane	( )	( )	_____
p) Methanol (wood alcohol)	( )	( )	_____
q) Toluene	( )	( )	_____
r) Carbon disulfide	( )	( )	_____
s) Glycol ethers (in paints or glue)	( )	( )	_____
t) Other Solvents	( )	( )	_____
u) Anesthetic gases	( )	( )	_____
v) Sterilizing agent/Fumigant	( )	( )	_____
w) Lead Arsenate Pesticide	( )	( )	_____
x) Organophosphate Pesticide	( )	( )	_____
y) Other Pesticide	( )	( )	_____
z) Other Chemical Exposure	( )	( )	

	Chemical	Dates (Start/Stop)
i)	_____	_____
ii)	_____	_____
iii)	_____	_____

17) Have you **ever** used any of the chemicals listed here or above in any of your other activities or hobbies?

	Chemical	Dates (Start/Stop)
a)	_____	_____
b)	_____	_____
c)	_____	_____

Pesticides, insecticides or weed killers:

	YES	NO	Dates (Start/Stop)
d) Sevin	( )	( )	_____
e)	_____		_____
f)	_____		_____
g)	_____		_____

Appendix 2. (b)

Health Questionnaire Part II
(with supplement)

HEALTH QUESTIONNAIRE PART II

Interviewer_____ Today's Date: ___ ___/___ ___/___ ___
month day year

Put label here

1 2 3 4 5
ID#

Please PRINT all your answers. The researchers will be glad to help you with any question you do not understand.

The following questions concern your family:

	YES	NO	
1. Have you ever been married (include common-law, living-as-married)?	( )	( )	7

2. How many times have you been married? _____ Times 8

3. Please check if you are currently: 9

Married to first wife ____
Married to second wife ____
Divorced or separated ____
Widowed ____
Other (explain) _____

	YES	NO	
4. Have you **ever** fathered any children?	( )	( )	10

* If you have **never** been married **and never** fathered any children
* please turn in this questionnaire.

THANK YOU VERY MUCH FOR YOUR COOPERATION

If you have been married and/or you have fathered children in the past, please answer the following questions regarding your **current** or **most recent** wife/partner:

5. Current or most recent wife's first and last name (print) _____

6. Wife's current address and phone number: 1. Same as yours ____
2. Deceased ____
3. If different from yours ____

(Please Print) _____
Number street

_____
City State Zip

Phone: (___) ___-____

7. Date of marriage (or beginning of life together): __/__ (Month/Year) __/__ 11 12 13 14

8. If widowed, separated or divorced, please give the date of the end of the marriage: __/__ (Month/Year) __/__ 15 16 17 18

9. When was your wife born? __/__ (Month/Year) __/__ 19 20 21 22

10. What is the highest level of education your wife has completed? __ __ 23 24

(circle the number of years completed)

Elementary	1 2 3 4 5 6 7 8
High School	9 10 11 12
College	13 14 15 16+

	YES	NO	
11. Has your wife **ever** been employed outside the home?	( )	( )	__ 25

If **NO** go to Question 14.

If **YES**, please complete the following occupational history:

12. Please note all jobs your wife has held, starting with her most recent job and proceeding backwards in time since she left school.

	COMPANY	JOB TITLE	YR START	YR STOP	
1)					__/__/__ 26 27 28 29 30 31
2)					__/__/__ 32 33 34 35 36 37
3)					__/__/__ 38 39 40 41 42 43
4)					__/__/__ 44 45 46 47 48 49
5)					__/__/__ 50 51 52 53 54

13. Has your wife **ever** worked with any of the following chemicals?

CHEMICAL	YES	NO	START	STOP	
a) Uranium	( )	( )	_____	_____	56 57 58 59 60
b) Lead	( )	( )	_____	_____	
c) Mercury	( )	( )	_____	_____	
d) Glycol ethers or Cellosolves (in certain paints/glues)	( )	( )	_____	_____	71 72 73 74 75
e) Solvents					76 77 78 79 80
which type? _____	( )	( )	_____	_____	
f) Insecticides/Weed killers	( )	( )	_____	_____	
g) Anesthetic gases	( )	( )	_____	_____	
h) Sterilizing agents	( )	( )	_____	_____	
i) Radiation/many x-rays	( )	( )	_____	_____	
j) Other _____	( )	( )	_____	_____	21 22 23 24 25

14. How many live-born babies has your current or most recent wife **ever** had? (Do not include her stepchildren or adopted children)
(If NONE, enter 0 and go to question 17) ___ ___ (children) 26 27

15. How many of your wife's children who were alive at birth had abnormalities or defects? ALL abnormalities or defects should be included even if you do not think they are relevent or if they were not discovered at birth. (If NONE, enter 0). ___ ___ (children) 28 39

16. How many of your wife's children who were alive at birth had a serious or long lasting illness during their childhood? (If NONE enter 0). ___ ___ (children) 30 31

17. How many miscarriages or stillborn babies (babies born dead) has your wife **ever** had? (If NONE enter 0). ___ ___ (number) 32 33

18. Have you **ever** had a vasectomy?
Yes ___ No ___ Don't Know ___ 34 35 36
If Yes: When? _____

19. Has your wife **ever** had a hysterectomy (removal of womb) or tubal ligation (tubes tied)?
Yes ___ No ___ Don't Know ___ 37 38 39
If Yes: When? _____

19.a) If your wife has had a hysterectomy, was this for cancer? YES ( ) NO ( ) 40

20. Was there **ever** a time when you and your wife tried for <u>one year or more</u> to have children but were <u>unsuccessful</u>? YES ( ) NO ( ) 41

If **NO**, go to question 23a Bottom of Page.

21. If **YES**, when was that? FROM:_____ (year) TO:_____ (year) __ __/__ __ (42 43 44 45)

22a. Did a doctor **ever** tell your wife that she had any problems that made it difficult for her to become pregnant?

Yes ___ No ___ Don't Know ___ (46)

22b. If YES, why? (check where appropriate):

		FROM:(yr)	TO:(yr)
___ 1. Irregular periods	If so, when?	_____	_____
___ 2. No periods	If so, when?	_____	_____
___ 3. Obstruction of birth canal	If so, when?	_____	_____
___ 4. Blocked tubes	If so, when?	_____	_____
___ 5. Cyst on the ovaries	If so, when?	_____	_____
___ 6. Pituitary problems	If so, when?	_____	_____
___ 7. Being very nervous, depressed, anxious	If so, when?	_____	_____
___ 8. Other_____	If so, when?	_____	_____
___ 10. More than one problem	If so, when?	_____	_____

(47 48 49 50 51 52)

22c. Did your wife **ever** have any children before she was married to you?

Yes ___ No ___ Don't Know ___ (53)

22d. If **YES**, when was the child born? (year)

Child #1 _____ __ __ (54 55)
Child #2 _____ __ __ (56 57)
Child #3 _____ __ __ (58 59)
Child #4 _____ __ __ (60 61)

23a. Did a doctor **ever** tell you that you had any problems that made it difficult for you to father children?

Yes ___ No ___ Don't Know ___ (62)

23b. If YES, why? (check where appropriate):

		FROM:(yr)	TO:(yr)
___ 1. Loss of interest in sex	If so, when?	_____	_____
___ 2. Impotence	If so, when?	_____	_____
___ 3. History of mumps or gonorrhea	If so, when?	_____	_____
___ 4. Blocked tubes	If so, when?	_____	_____
___ 5. Undescended testicle	If so, when?	_____	_____
___ 6. Being very nervous, depressed, anxious	If so, when?	_____	_____
___ 7. Prostate problems	If so, when?	_____	_____
___ 8. Varicocele	If so, when?	_____	_____
___ 10. Other _____	If so, when?	_____	_____
___ 11. More than one problem	If so, when?	_____	_____

(63 64 65 66 67 68)

24. Has your wife **ever** smoked cigarettes regularly? YES ( ) NO ( ) 69

If **NO**, go to question 26 Next Page.

If **YES**, to question 24:

25a. Does your wife smoke cigarettes now?

YES ___ NO ___ DOES NOT APPLY ___ 70

If **NO** or '**DOES NOT APPLY**' go to question 25f.

If **YES** proceed with question 25b:

25b. Circle how many cigarettes/day your wife smokes now:

1	1-9
2	10-19
3	20-29
4	30-39
5	40 or more

71

25c. How old was your wife when she started smoking? _____ (years) 72 73

25d. How many years has your wife smoked regularly? _____ (years) 74 75

25e. On the average, of the entire time your wife has smoked, how many cigarettes/day has she smoked?

1	1-9
2	10-19
3	20-29
4	30-39
5	40 or more

76

If your wife still smokes now, please go to question 26 Next Page.

If your wife smoked in the past, but she does not smoke now because she quit smoking or she is deceased:

25f. If your wife has quit smoking or she is deceased, how old was she the last time she stopped? _____ (years) 77 78

25g. How many years did your wife smoke cigarettes regularly?

_____ (years) 79 80 ★

25h. On the average, of the entire time your wife smoked, how many cigarettes/day did she smoke?

1	1-9
2	10-19
3	20-29
4	30-39
5	40 or more

1

26. Has your wife **ever** drunk alcoholic beverages?	YES ( ) NO ( )	2

If **NO** go to question 29 Next Page.

If YES to 26:

27a. Does your wife presently drink alcoholic beverages? YES ___ NO ___ DOES NOT APPLY___		3

If **NO** or "**DOES NOT APPLY**" go to question 28a.

If YES to question 27a:

27b. How often on average does your wife drink alcoholic beverages? 4

( ) 6-7 days/week[5]
( ) 3-5 days/week[4]
( ) 1-2 days/week[3]
( ) Less than once/week but more than once/month[2]
( ) Less than once/month[1]

27c. When your wife drinks, how many drinks does she average in one sitting? 5

( ) 1 drink[1] ( ) 3 drinks[3] ( ) 6-7 drinks[5]
( ) 2 drinks[2] ( ) 4-5 drinks[4] ( ) 8 or more drinks[6]

27d. How long has your wife been drinking the above amount? _____years. 6 7

27e. Give the average number of each beverage that your wife drinks in <u>one week</u>:(Leave the space blank if she does not drink that type of alcoholic beverage once/week):

___ Beer (12 oz. bottles or cans) 8 9
___ Wine (glasses) 10 11
___ Alcoholic drinks (shots of hard liquor) 12 13

28a. Has your wife ever <u>in the past</u> been a heavier drinker than she is now?	YES ( ) NO ( )	14

If **NO** go to question 29 next page.

If YES to question 28a:

28b. How often on average did your wife drink alcoholic beverages? 15

( ) 6-7 days/week[5]
( ) 3-5 days/week[4]
( ) 1-2 days/week[3]
( ) Less than once/week but more than once/month[2]
( ) Less than once/month[1]

28c. When your wife drank alcoholic beverages how many drinks did she average in one sitting?

( ) 1 drink[1] ( ) 3 drinks[3[( ) 6-7 drinks[5]
( ) 2 drinks[2] ( ) 4-5 drinks[4] ( ) 8 or more drinks[6] 16

28d. During what years did your wife drink the above amount?

year started _____ year stopped _____ __/__ __
17 18 19 20

---

29. Has your wife **ever** been hospitalized for or has a doctor ever told her that she had any of the following conditions or diseases?

	YES	NO	START	STOP	21 22 23 24 25
a) Tuberculosis	( )	( )	_____	_____	__/__ __/__ __
b) Cancer, leukemia, or brain tumor	( )	( )	_____	_____	__/__ __/__ __ 30
c) Epilepsy, seizures, or convulsions	( )	( )	_____	_____	__/__ __/__ __ 35
d) Anemia (low blood count)	( )	( )	_____	_____	__/__ __/__ __ 40
e) Syphilis	( )	( )	_____	_____	__/__ __/__ __ 45
f) High blood pressure	( )	( )	_____	_____	__/__ __/__ __ 50
g) Kidney disease	( )	( )	_____	_____	__/__ __/__ __ 55
h) Diabetes	( )	( )	_____	_____	__/__ __/__ __ 60
i) Surgery requiring hospitalization (explain)_____	( )	( )	_____	_____	__/__ __/__ __ 61 62 63 64 65
j) Serious heart problems	( )	( )	_____	_____	__/__ __/__ __ 70
k) Thyroid problems	( )	( )	_____	_____	__/__ __/__ __ 75
l) Psychological problems (bad nerves)	( )	( )	_____	_____	__/__ __/__ __ ★
m) Other_____	( )	( )	_____	_____	__/__ __/__ __ 1 2 3 4 5

30. Please list any medicines your wife may have taken during her illness(es):

NAME OF MEDICINE (or reason for taking)	YEAR START	YEAR STOP	
a)_____	_____	_____	__ __ __/__ __/__ __ 6 7 8 9 10 11 12
b)_____	_____	_____	__ __ __/__ __/__ __ 13 14 15 16 17 18 19
c)_____	_____	_____	__ __ __/__ __/__ __ 20 21 22 23 24 25 26
d)_____	_____	_____	__ __ __/__ __/__ __ 27 28 29 30 31 32 33
e)_____	_____	_____	__ __ __/__ __/__ __ 34 35 36 37 38 39 40

31. About how much money do you make per year in your current job, or if you are retired, did you make on your most recent job?

1. $0 -$ 9,999 ____
2. $10,000-$19,999 ____
3. $20,000-$29,999 ____
4. $30,000 or more ____

41

32. About how much money does your wife make per year in her current job or if she is retired or no longer with you, did she make on her most recent job?

No earnings (not working outside of home) ____

1. $ 1,000 -$ 9,999 ____
2. $10,000-$19,999 ____
3. $20,000-$29,999 ____
4. $30,000 or more ____

42

33. Is it alright with you if we contact your wife or ex-wife to ask her a few questions about your children? YES ( ) NO ( )

43

This completes the questionnaire. However, **if you were married more than once**, please see the research person to obtain the necessary additional form(s). When you have completed all the forms as best you can, the research person would like to see you to go over some of the questions with you.

THANK YOU VERY MUCH FOR YOUR INTEREST AND COOPERATION

HAVE A NICE DAY!

SUPPLEMENT TO HEALTH QUESTIONNAIRE PART II, Q 14

INTERVIEWER _____

SUBJECT'S NAME _____

14(S). Please give the following information about your wife's children who were alive at birth. Start with the first child born:

Child	1 (oldest)	2	3	4	5	6	7	8
First name								
a. SEX (Male, Female)	M___ F___	M___ F___	M___ F___	M___ F___	M___ F___	M___ F___	M___ F___	M___ F___
b. Date of birth (MO/DAY/YR)	___/___/___	___/___/___	___/___/___	___/___/___	___/___/___	___/___/___	___/___/___	___/___/___
c. Weight at birth (lbs. oz.)	_____	_____	_____	_____	_____	_____	_____	_____
d. Was this baby premature?	YES _____ if yes, how many weeks? ____(WKS) NO _____	YES _____ if yes, how many weeks? ____(WKS) NO _____	YES _____ if yes, how many weeks? ____(WKS) NO _____	YES _____ if yes, how many weeks? ____(WKS) NO _____	YES _____ if yes, how many weeks? ____(WKS) NO _____	YES _____ if yes, how many weeks? ____(WKS) NO _____	YES _____ if yes, how many weeks? ____(WKS) NO _____	YES _____ if yes, how many weeks? ____(WKS) NO _____
e. Was this baby: 1. normal birth 2. caesarian sect.	1. ___ 2. ___	a. ___ b. ___	a. ___ b. ___	a. ___ b. ___	a. ___ b. ___	a. ___ b. ___	a. ___ b. ___	a. ___ b. ___
f. Is this child still alive?	YES__ NO__	YES__ NO__	YES__ NO__	YES__ NO__	YES__ NO__	YES__ NO__	YES__ NO__	YES__ NO__
g. If no longer alive, what was the cause of death?								
h. If no longer alive, when did he/she die?	___ ___ MO YR	___ ___ MO YR	___ ___ MO YR	___ ___ MO YR	___ ___ MO YR	___ ___ MO YR	___ ___ MO YR	___ ___ MO YR

Appendix 3

Listing of Variables

Listing of Variables

MERCURY EXPOSURE VARIABLES

VARIABLE	#CASES	LEVELS
2.HGSTATUS	584	3
VOLUNTEER(1) EXPOSED(2) NON-EXPOSED(3)		
119.HGU-LEQU	584	
120.MERCURY ADDED	584	2
ADDED(1) NOTADDED(2)		
121.MERCURY EARLY	584	2
EARLY(1) NOTEARLY(2)		
122.HG DURATION	584	
123.HG PAV (0.3 MG/L)	584	
124.HG PAV2 (O.6 MG/L)	584	
125.HG HIGHEST PEAK	584	
126.HG AVERAGE	584	
128.UHG YEAR START	584	
129.UHG MONTH START	584	
130.UHG DAY START	584	
131.UHG YEAR STOP	584	
132.UHG MONTH STOP	584	
133.UHG DAY STOP	584	
134.HG YEARS WORKED	584	
135.HGU RATE	584	
136.YEARS NO HG	584	

ORAU Data

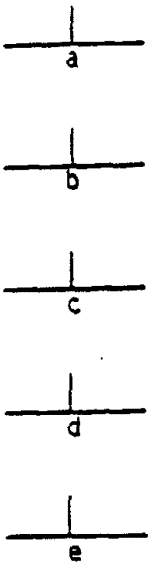
VARIABLE	#CASES	LEVELS
1.ID	584	999999
101.STATUS	584	3
ACTIVE(1) RETIRED(2) TERMINATED(3)		
102.PAY	584	3
HOURLY(1) WEEKLY(2) MONTHLY(3)		
114.LEAD NUMBER	584	
115.LEAD FIRST DATE	584	
116.LEAD LAST DATE	584	

SUPPLEMENT TO HEALTH QUESTIONNAIRE PART II, Q 15 & 16

SUBJECT'S NAME _____

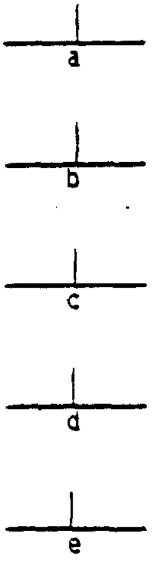
15(S). Please give the following information about your wife's children with an abnormality/defect (check where appropriate):

Child	1(a)	2(b)	3(c)	4(d)	5(e)
Name:					
Abnormalities or defects (check those that apply):					
01. Down's syndrome (Mongoloid)					
02. Cleft palate					
03. Club foot					
04. Heart defect					
05. Kidney defect					
06. Other (specify):					
07. > one defect					



16(S). Please give the following information about your wife's children who had serious childhood illnesses (check where appropriate):

Child	1(a)	2(b)	3(c)	4(d)	5(e)
Name:					
Serious childhood illnesses (check those that apply:					
01. Cancer					
02. Kidney problems					
03. Nervous problems					
04. Mental retardation					
05. Small for age					
06. Surgery as child					
07. Failed grade or in special education					
08. Other (explain):					
09. > one defect					



SUPPLEMENT TO HEALTH QUESTIONNAIRE PART II, Q 15 & 16

SUBJECT'S NAME _____

17(S). Please give the following information about your wife's miscarriages or stillborn babies:

Miscarriage or stillbirth	1. time (a)	2. time (b)	3. time (c)	4. time (d)
Year	19___	19___	19___	19___
How many months pregnant was your wife at the time?	Months pregnant:___	Months pregnant:___	Months pregnant:___	Months pregnant:___

a ___

b ___

c ___

d ___

Subject reliability (interviewer estimation):

1. ____ poor
2. ____ fair
3. ____ good
4. ____ excellent

___

Reproductive Questionnaire

VARIABLE	#CASES	LEVELS
2002.MARTIMES	584	8
2006.MARSTAYR	584	99
2008.MARSTOYR	584	99
2011.WEDUC	584	99
2012.WCUREMPL	584	9
YES(1) NO(2) NA(8) DK(9)		
2062.VASECTOM	584	9
YES(1) NO(2) DK(9)		
2064.HYSTEREC	584	9
YES(1) NO(2) DK(9)		
2067.CPINFERT	584	9
YES(1) NO(2) DK(9)		
2084.WEVERSMK	584	9
YES(1) NO(2) DK(9)		
2093.WEVERDRK	584	9
YES(1) NO(2) DK(9)		
2183.CH1SEX	584	9
MALE(1) FEMALE(2)		
2184.CH1BRMO	584	99
DK(99)		
2185.CH1BRDA	584	99
DK(99)		
2186.CH1BRYR	584	99
DK(99)		
2187.CH1BWTLB	584	99
DK(99)		
2188.CH1BWTOZ	584	99
DK(99)		
2189.CH1PREM	584	9
YES(1) NO(2) DK(9)		
2190.CH1PREWK	584	99
NA(88) DK(99)		
2191.CH1BIRTH	584	9
NORMAL(1) CAESAR(2) DK(9)		
2192.CH1ALIVE	584	9
YES(1) NO(2) DK(9)		
2193.CH1CDETH	584	99
NA(88) DK(99)		
2194.CH1DTHMO	584	99
NA(88) DK(99)		
2195.CH1DTHYR	584	99
NA(88) DK(99)		
2290.WAGEMAR	584	54
2292.LB REAL	584	
2293.ABNREAL	584	
2294.ILLREAL	584	
2295.SA REAL	584	
2296.TOTPREG	584	
2302.SATOTP%	584	
2303.ABNTLB%	584	

2304.ILLTLB%	584	

OUTCOME VARIABLES

Behavioral Tests

VARIABLE	#CASES	LEVELS
ONEHOLE TEST		
4177.AVE # PINS	584	
4178.SQ AVE # PINS	584	
4179.AVE GRASPTM	584	
4181.AVE MOVETM	584	
4183.AVE POSITIONTM	584	
4185.AVE REACHTM	584	
4187.AVE TM GR FUMBLE	584	
4189.AVE TM PS FUMBLE	584	
4191.AVE # GR FUMBLE	584	
4193.AVE # PS FUMBLE	584	
DIGIT SPAN TEST		
4202.DIGIT SPAN	584	
MOOD SCALE		
4302.M TENSION	584	
4304.M DEPRESS		584
4306.M ANGER	584	
4308.M FATIGUE	584	
4310.M CONFUSE	584	
4312.MOODSCORE	584	
VOCABULARY		
4403.VOCAB # CORRECT	584	
REACTION TIME		
4568.AVE REACTION TM	584	
4569.INV AVE RT	584	
VISUAL MEMORY		
4603.VM # CORRECT	584	
4616.VM % CORRECT	584	
4618.AVE TIME VM	584	
SYMBOL DIGIT		
4718.SD MEAN # CORRECT	584	
4719.SD % CORRECT	584	
4721.SD AVE TIME	584	
HAND-EYE COORDINATION		
4810.MEAN HE	584	
4811.INV MEAN HE	584	
CRITICAL TRACKING TEST		
4922.TRACKING MEAN	584	
4924.LOG TRACK MEAN	584	

Health Questionnaire

VARIABLE	#CASES	LEVELS
4.MONTH	584	9
J85(1) OCT(2) DEC(3) MAR(4) J86(5) SEP(6)		
5.JOBCODE	584	9
UNSKILLED(1) SEMISKILLED(2) SKILLED(3) FOREMAN(4) OFFICE(5)		
ENGINEER(6)		
6.AGE	584	
1001.INTERVIEWER	584	9
KA(1) KB(2) LF(3) GL(4) MD(9)		
1002.DATE	584	
1003.BIRRTHDATE	584	
1004.EDUCATION	584	
1005.BIRTHPLACE	584	1006
USA(1) OTHER(2) MD(9)		
1006.ENGLISH	584	9
ENGLISH(1) OTHER(2) MD(9)		
1007.HEADINJURY	584	9
YES(1) NO(2) MD(9)		
1008.TUBERCULOSIS	584	9
YES(1) NO(2) MD(9)		
1009.CANCER	584	9
YES(1) NO(2) MD(9)		
1400.CANCER TYPE	584	10
SKIN(1) PROSTATE(2) BLADDER(3) LUNG(4) STOMACH(5) LIVER(6)		
CLL(7) PANCREAS(8) OTHER(9) MISS(10)		
1010.EPILEPSY	584	9
YES(1) NO(2) MD(9)		
1011.ANEMIA	584	9
YES(1) NO(2) MD(9)		
1012.POLIO	584	9
YES(1) NO(2) MD(9)		
1013.SYPHILIS	584	9
YES(1) NO(2) MD(9)		
1014.HYPERTENSION	584	9
YES(1) NO(2) MD(9)		
1015.TREATMENT HYPTN	584	9
YES(1) NO(2) MD(9)		
1016.KIDNEY	584	9
YES(1) NO(2) MD(9)		
1017.ENCEPH	584	9
YES(1) NO(2) MD(9)		
1018.MS	584	9
YES(1) NO(2) MD(9)		
1019.PARKINSONS	584	9
YES(1) NO(2) MD(9)		
1020.OTHER CNS	584	9
YES(1) NO(2) MD(9)		
1021.DIABETES	584	9
YES(1) NO(2) MD(9)		

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1022.FAMILY DIABETES          584        9
   YES(1) NO(2) MD(9)
1027.TREMOR                   584        9
   YES(1) NO(2) MD(9)
1028.FAMILY TREMOR            584        9
   YES(1) NO(2) MD(9)
1033.SURGERY                  584        9
   YES(1) NO(2) MD(9)
1034.HEART PROBLEM            584        9
   YES(1) NO(2) MD(9)
1035.THRYOID                  584        9
   YES(1) NO(2) MD(9)
1040.MEDICATION               584        9
   YES(1) NO(2) MD(9)
1085.CAFFEINE                 584        9
   YES(1) NO(2) MD(9)
1089.EVER SMOKED              584        9
   YES(1) NO(2) MD(9)
1090.SMOKE NOW                584        9
   YES(1) NO(2) MD(9)
1091.AMOUNT SMOKED1           584       99
   05_CIG(5) 15_CIG(15) 25_CIG(25) 35_CIG(35) 45_CIG(45)
   MD(99)
1098.EVER DRINK               584        9
   YES(1) NO(2) MD(9)
1099.DRINK NOW                584        9
   YES(1) NO(2) MD(9)
1109.YEARS DRINK2             584
1110.DRINKING PROBLEM         584        9
   YES(1) NO(2) MD(9)
1320.DRINKS/WEEK1             584
1321.DRINKS/WEEK              584
1322.DRINKS/WEEK2             584
1151.URANIUM                  584        9
   YES(1) NO(2) MD(9)
1163.MERCURY                  584        9
   YES(1) NO(2) MD(9)
1166.LEAD                     584        9
   YES(1) NO(2) MD(9)
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Neurological Examination

VARIABLE	#CASES	LEVELS
6001.EXAMINER	584	9
JA(1) PD(2)		
6002.INTERVIEW ORDER	584	9
FIRST(1) SECOND(2) ONLY(3)		
6003.GUMS	584	9
SEVERE(1) MOD(2) MILD(3) TRACE(4) NONE(5)		
6004.PROXIMAL STRENGTH	584	9
SEVERE(1) MOD(2) MILD(3) TRACE(4) NONE(5)		
6005.DISTAL STRENGTH	584	9
SEVERE(1) MOD(2) MILD(3) TRACE(4) NONE(5)		
6006.SUSTENSION TREM	584	9
SEVERE(1) MOD(2) MILD(3) TRACE(4) NONE(5)		
6007.ARMS	584	9
SEVERE(1) MOD(2) MILD(3) TRACE(4) NONE(5)		
6008.LEGS	584	9
SEVERE(1) MOD(2) MILD(3) TRACE(4) NONE(5)		
6009.GRIP STRENGTH	584	
6010.NUMBER OF TEETH	584	
6011.JOINT POSITION IND	584	
6012.JOINT POSITION TOE	584	
6013.PIN-PAIN ARM	584	
6014.PIN-PAIN LEG	584	
6015.2-POINT DISC INDEX	584	
6016.2-POINT DISC FOOT	584	
6017.TOUCH SENSATION	584	
6018.TOUCH SENSE FOOT	584	
6019.VIBRATION INDEX	584	
6020.VIBRATION FOOT	584	
6021.BICEPS	584	9
ABSENT(1) MOD1(2) SI1(3) NORMAL(4) SI2(5) MOD2(6) HYPER(7)		
6022.BRACHI	584	9
ABSENT(1) MOD1(2) SI1(3) NORMAL(4) SI2(5) MOD2(6) HYPER(7)		
6023.QUAD	584	9
ABSENT(1) MOD1(2) SI1(3) NORMAL(4) SI2(5) MOD2(6) HYPER(7)		
6024.ACHILLES	584	9
ABSENT(1) MOD1(2) SI1(3) NORMAL(4) SI2(5) MOD2(6) HYPER(7)		
6025.BABINSKI	584	9
POSITIVE(1) NONE(2)		
6026.JAW	584	9
POSITIVE(1) NONE(2)		
6027.SNOUT REFLEX	584	9
POSITIVE(1) NONE(2)		
6028.DORSPED	584	9
ABSENT(1) DECR(2) NORMAL(3)		
6029.NORMAL EXAM	584	9
YES(1) NO(2)		

6030.POLYNEUROPATHY	584	9
YES(1) EQUIV(2) NO(3)		
6031.ABNORMAL TREMOR	584	9
YES(1) EQUIV(2) NO(3)		
6032.OTHER NEURO	584	9
YES(1) EQUIV(2) NO(3)		
6170.NEOPLASM	584	2
YES(1) NO(2)		
6171.TRAUMA	584	2
YES(1) NO(2)		
6172.TOXIC EXPOSURE	584	2
YES(1) NO(2)		
6173.STRUCTURAL	584	2
YES(1) NO(2)		
6174.UNKNOWN	584	2
YES(1) NO(2)		
6175.VASCULAR	584	2
YES(1) NO(2)		
6176.PSYCHIATRIC	584	2
YES(1) NO(2)		
6177.CONNECTIVE TISSUE	584	2
YES(1) NO(2)		
6178 INFLAMMATORY	584	2
YES(1) NO(2)		
6179.METABOLIC	584	2
YES(1) NO(2)		
6180.NUTRITIONAL	584	2
YES(1) NO(2)		

Electrodiagnostic Evaluation

VARIABLE	#CASES	LEVELS
7001.HEIGHT	584	
7002.WEIGHT	584	
7007.SURAL AMP	584	
7008.SURAL DL	584	
7009.TIBIAL AMP	584	
7010.TIBIAL DL	584	
7011.TIBIAL PA	584	
7012.TIBIAL CV	584	
7013.MEDIAN SN AMP	584	
7014.MEDIAN SN DL	584	
7015.MEDIAN SN PA	584	
7016.MEDIAN SN CV	584	
7017.ULNAR SN AMP	584	
7018.ULNAR SN DL	584	
7019.ULNAR SN PA	584	
7020.ULNAR SN CV	584	
7021.ULNAR MT AMP	584	
7022.ULNAR MT DL	584	
7023.ULNAR MT PA	584	
7024.ULNAR MT CV	584	
7025.POLYNEUROPATHY	584	3
NORMAL(1) EQUIV(2) POLY(3)		
7026.MONONEUROPATHY	584	3
NONE(1) MONO(2) OTHER(3)		
7027.MOTOR NRVS ABN	584	
7028.SENSORY NRVS ABN	584	
7029.MT AMP LL	584	
7030.MT AMP NM	584	
7031.MT CV LL	584	
7032.MT CV NM	584	
7033.MT TMCV LL	584	
7034.MT TMCV NM	584	
7035.SN AMP LL	584	
7036.SN AMP NM	584	
7037.SN CV LL	584	
7038.SN CV NM	584	
7039.SN TMCV LL	584	
7040.SN TMCV NM	584	

Quantitative Tremor Test

VARIABLE	#CASES	LEVELS
8031.ACC RMS	584	
8032.ACC AVE AMP	584	
8034.DISP RMS	584	
8035.DISP AVE AMP	584	

Urinary Measures

VARIABLE	#CASES	LEVELS
9001.PROTEIN	584	
9002.CREATININE	584	
9003.ALBUMIN	584	
9004.GLUCOSAMINIDASE	584	
9005.URINARY MERCURY	584	
9016.LOG PRO/CREAT	584	
9017.LOG ALB/CREAT	584	
9018.LOG BNAG/CREAT	584	

Appendix 4

Description of Variables

Description of Variables

MERCURY EXPOSURE VARIABLES

VARIABLE	N	MIN	MAX	MEAN	STD DEV
2.HGSTATUS	502	2.0000	3.0000	2.5080	.50044
119.HGU	502	0.	8572.0	1768.7	1982.9
120.MERADD	429	1.0000	2.0000	1.9930	.83429 -1
121.MEREARL	429	1.0000	2.0000	1.9184	.27405
122.HGDUR	502	0.	51.000	10.363	12.236
123.HGPAV	502	0.	13.000	1.7430	2.4890
124.HGPAV2	502	0.	6.0000	.36653	.80982
125.HGPEAK	502	0.	3022.0	318.48	414.62
126.HGAVE	502	0.	719.00	131.72	162.81
128.UHGYRST	248	1953.0	1958.0	1954.2	.90476
129.UHGMONST	248	1.0000	12.000	6.4879	3.1301
130.UHGDAYST	248	1.0000	30.000	15.887	8.5169
131.UHGYRSP	248	1955.0	1972.0	1961.6	3.8058
132.UHGMONSP	248	1.0000	12.000	5.7339	3.3935
133.UHGDAYSP	248	1.0000	31.000	14.520	8.1424
134.HGYRSWRK	243	0.	19.000	7.4979	3.9818
135.HGURATE	242	64.804	695.75	200.87	103.63
136.YRSNOHG	242	14.000	30.000	24.302	3.8158

ORAU Data

VARIABLE	N	MIN	MAX	MEAN	STD DEV
1.ID	502	70185.	.90007 +6	.12907 +6	36756.
101.STATUS	486	1.0000	3.0000	1.6029	.55679
102.PAY	192	1.0000	3.0000	1.1875	.54748
114.LEADNO	502	0.	90.000	.86454	6.0058
115.LFDATE	68	.19581 +8	.19740 +8	.19632 +8	44917.
116.LLDATE	68	.19581 +8	.19741 +8	.19652 +8	52783.

HEALTH QUESTIONNAIRES

Health Questionnaire

VARIABLE	N	MIN	MAX	MEAN	STD DEV
4.MONTH	502	1.0000	6.0000	3.3566	1.4305
5.JOBCODE	435	1.0000	6.0000	2.9586	1.0854
6.AGE	502	50.000	90.000	64.243	7.2830
1001.INTER	371	1.0000	6.0000	1.7871	.92148
1002.DATE	483	0.	.12139 +6	66730.	40017.
1003.BRTHDATE	501	10126.	.12313 +6	67816.	34694.
1004.EDUCAT	502	2.0000	16.000	11.719	2.5381
1005.BRTPLACE	501	1.0000	2.0000	1.0020	.44677 -1
1006.ENGLISH	501	1.0000	1.0000	1.0000	
1007.HEADINJ	501	1.0000	2.0000	1.8683	.33854
1008.TUBERCU	501	1.0000	2.0000	1.9880	.10889
1009.CANCER	501	1.0000	2.0000	1.9082	.28906
1400.CANCTYPE	46	1.0000	10.000	4.3043	3.3124
1010.EPILEPSY	501	1.0000	2.0000	1.9860	.11749
1011.ANEMIA	501	1.0000	2.0000	1.9461	.22603
1012.POLIO	501	1.0000	2.0000	1.9860	.11749
1013.SYPH	501	1.0000	2.0000	1.9980	.44677 -1
1014.HYPTEN	501	1.0000	2.0000	1.6028	.48981
1015.TRHYPTN	469	1.0000	2.0000	1.6162	.48683
1016.KIDNEY	500	1.0000	2.0000	1.8960	.30557
1017.ENCEPH	500	1.0000	2.0000	1.9900	.99598 -1
1018.MS	501	2.0000	2.0000	2.0000	
1019.PARKIN	501	1.0000	2.0000	1.9980	.44677 -1
1020.OTHERCNS	501	1.0000	2.0000	1.9202	.27132
1021.DIABETES	500	1.0000	2.0000	1.8840	.32055
1022.FAMDIA	501	1.0000	2.0000	1.7146	.45207
1027.TREMOR	501	1.0000	2.0000	1.9182	.27439
1028.FAMTREM	500	1.0000	2.0000	1.9380	.24140
1033.SURG	437	1.0000	2.0000	1.2174	.41294
1034.HEART	437	1.0000	2.0000	1.7689	.42203
1035.THRYOID	437	1.0000	2.0000	1.9497	.21890
1085.CAFFEINE	501	1.0000	2.0000	1.0519	.22204
1089.EVERSMK	500	1.0000	2.0000	1.2180	.41330
1090.SMKNOW	403	1.0000	2.0000	1.7146	.45215
1091.AMTSMK1	115	5.0000	45.000	25.000	10.842
1098.EVERDRK	500	1.0000	2.0000	1.3940	.48912
1099.DRKNOW	301	1.0000	2.0000	1.5083	.50076
1109.YRSDRK2	176	0.	50.000	13.830	12.392
1110.DRKPROB	323	1.0000	2.0000	1.9474	.22364
1320.DRKSWK1	148	1.0000	25.000	6.3311	4.9023
1321.DRKSWEEK	126	0.	50.000	8.1349	8.6110
1322.DRKSWK2	169	1.0000	30.000	8.4024	4.8173
1151.URANIUM	501	1.0000	2.0000	1.1277	.33414
1163.MERCURY	501	1.0000	2.0000	1.3293	.47044
1166.LEAD	501	1.0000	2.0000	1.5549	.49747

Reproductive Questionnaire

VARIABLE	N	MIN	MAX	MEAN	STD DEV
2002.MARTIMES	495	1.0000	5.0000	1.2424	.56717
2006.MARSTAYR	494	22.000	82.000	45.609	7.5754
2008.MARSTOYR	86	38.000	86.000	72.628	9.8447
2011.WEDUC	491	4.0000	16.000	11.593	2.2051
2012.WCUREMPL	494	1.0000	2.0000	1.2146	.41094
2062.VASECTOM	490	1.0000	2.0000	1.8531	.35441
2064.HYSTEREC	492	1.0000	2.0000	1.5061	.50047
2067.CPINFERT	493	1.0000	2.0000	1.8803	.32491
2084.WEVERSMK	494	1.0000	2.0000	1.6154	.48700
2093.WEVERDRK	493	1.0000	2.0000	1.8215	.38332
2183.CH1SEX	447	1.0000	2.0000	1.5190	.50020
2184.CHI1BRMO	407	1.0000	12.000	6.6388	3.2362
2185.CHI1BRDA	354	1.0000	31.000	14.492	9.0326
2186.CHI1BRYR	446	24.000	69.000	47.738	7.6869
2187.CH1BWTLB	418	2.0000	12.000	7.2057	1.3432
2188.CH1BWTOZ	266	1.0000	15.000	7.7444	3.1781
2189.CHI1PREM	444	1.0000	2.0000	1.9324	.25129
2190.CH1PREWK	21	1.0000	12.000	5.6667	3.1833
2191.CH1BIRTH	446	1.0000	2.0000	1.0650	.24684
2192.CH1ALIVE	447	1.0000	2.0000	1.0559	.23004
2193.CH1CDETH	22	77.000	77.000	77.000	
2194.CH1DTHMO	12	1.0000	11.000	5.6667	3.4989
2195.CH1DTHYR	23	36.000	85.000	56.609	16.172
2290.WAGEMAR	491	14.000	54.000	21.422	4.8369
2292.LB REAL	495	0.	13.000	2.4586	1.7102
2293.ABNREAL	495	0.	5.0000	.19192	.51055
2294.ILLREAL	495	0.	4.0000	.30909	.64216
2295.SA REAL	495	0.	6.0000	.34141	.74922
2296.TOTPREG	495	0.	15.000	2.8000	1.9127
2302.SATOTP%	459	0.	100.00	10.587	21.510
2303.ABNTLB%	448	0.	100.00	7.3211	18.409
2304.ILLTLB%	448	0.	100.00	13.075	25.764

OUTCOME VARIABLES

Behavioral Tests

VARIABLE	N	MIN	MAX	MEAN	STD DEV
ONEHOLE TEST					
4177.AVEPINS	490	1.0000	44.500	27.609	7.1730
4178.SQAVEPIN	490	1.0000	1980.3	813.59	369.07
4179.AVEGRASP	489	.26250	-110.880	.30478	.63225
4181.AVEMOVE	489	.48775	8.3190	.81015	.41547
4183.AVEPOS	489	.13250	-126.381	.66302	1.7932
4185.AVEREACH	489	.30350	2.5905	.61190	.24686
4187.AVTMGF	491	.72500	-2 5.6230	.11629	.40362
4189.AVTMPF	489	.32500	-2 1.4565	.11099	.20722
4191.AVNUMGF	491	1.2500	72.000	13.996	9.5605
4193.AVNUMPF	489	.25000	71.250	13.372	8.8562
DIGIT SPAN TEST					
4202.DSPAN1	488	2.7373	8.9051	5.5014	.98275
MOOD SCALE					
4302.MTENSION	494	1.0000	4.8000	2.4235	.70634
4304.MDEP	494	1.0000	4.8000	1.8255	.66467
4306.MANGER	494	1.0000	4.4000	1.6947	.60499
4308.MFATIGUE	494	1.0000	4.8000	2.8449	.76887
4310.MCONFUSE	494	1.0000	4.8000	2.2947	.61312
4312.MOODSCOR	494	5.4000	21.600	11.083	2.5650
VOCABULARY					
4403.VOCNCOR	494	4.0000	25.000	16.447	4.6722
REACTION TIME					
4568.AVEREACT	478	277.80	631.90	375.37	56.916
4569.INVAVERT	478	.15825	-2.35997	-2.27174 -2	.36013 -3
VISUAL MEMORY					
4603.VMNCORR	491	2.0000	12.000	8.4216	2.1484
4616.VMPCCOR	491	16.667	100.00	70.180	17.904
4618.AVETMVM	491	3.1091	30.373	8.2936	3.2355
SYMBOL DIGIT SUBSTITUTION					
4718.SDMNNMCR	492	5.5000	9.0000	8.7236	.48059
4719.SDPCCOR	492	61.111	100.00	96.929	5.3399
4721.AVETMSD	492	2.0222	9.9778	3.6736	1.1882
HAND-EYE COORDINATION					
4810.MEANHE	494	3.3733	31.060	7.6544	3.7570
4811.INVMNHE	251	.40236 -1	.28818	.15982	.52754 -1
CRITICAL TRACKING					
4922.STMEAN	429	.16600	.78800	.32331	.70773 -1
4924.LOGSTMN	429	-.77989	-.10347	-.50059	.94949 -1

Neurological Examination

VARIABLE	N	MIN	MAX	MEAN	STD DEV
6001.IINTER	501	1.0000	2.0000	1.4930	.50045
6002.ORDER	226	1.0000	3.0000	2.6814	.73352
6003.GUMS	501	2.0000	5.0000	4.8323	.49783
6004.PROX	500	2.0000	5.0000	4.9780	.21356
6005.DIST	500	1.0000	5.0000	4.9500	.30279
6006.TREMOR	500	1.0000	5.0000	4.5940	.71146
6007.ARMS	500	2.0000	5.0000	4.8040	.47963
6008.LEGS	498	1.0000	5.0000	4.9558	.28023
6009.GRIP	500	12.000	66.000	43.462	8.5127
6010.TEETH	501	0.	33.000	12.619	11.746
6011.JPSIND	498	0.	2.0000	.20080	-1 .15408
6012.JPSTOE	498	0.	10.000	.24096	.98997
6013.PINARM	500	50.000	1000.0	183.02	110.59
6014.PINLEG	498	0.	700.00	126.39	79.698
6015.DISCIND	500	2.0000	19.000	4.5690	1.7326
6016.DISCFOOT	496	10.000	200.00	33.311	14.942
6017.TOUCH	498	2.3600	4.7400	3.5596	.40084
6018.TOUCHTO	498	2.4400	6.6500	3.8641	.48868
6019.VIBIND	499	1.0000	17.000	8.3898	2.9146
6020.VIBTOE	496	4.0000	30.000	15.732	5.0029
6021.BICEPS	501	1.0000	7.0000	3.9242	.98094
6022.BRACHI	501	1.0000	7.0000	3.8184	.99847
6023.QUAD	501	1.0000	7.0000	4.2954	.92334
6024.ACH	501	1.0000	7.0000	3.5269	1.2107
6025.BABIN	495	1.0000	2.0000	1.0263	.16008
6026.JAW	496	1.0000	2.0000	1.0786	.26943
6027.SUCK	500	1.0000	2.0000	1.3820	.48636
6028.DORSPED	492	1.0000	3.0000	2.7744	.54894
6029.EXAM	499	1.0000	2.0000	1.5210	.50006
6030.POLY	501	1.0000	3.0000	2.5349	.74383
6031.ABTREM	501	1.0000	3.0000	2.5848	.66880
6032.OTHERN	500	1.0000	3.0000	2.4080	.91170
6170.CANCER	496	1.0000	2.0000	1.9839	.12610
6171.TRAUMA	496	1.0000	2.0000	1.9879	.10943
6172.TOXINS	496	1.0000	2.0000	1.9778	.14741
6173.STRUCTUR	496	1.0000	2.0000	1.9698	.17143
6174.UNKNOWN	496	1.0000	2.0000	1.9476	.22310
6175.NEURVAS	496	1.0000	2.0000	1.9819	.13361
6176.PSYCH	496	1.0000	2.0000	1.9940	.77614 -1
6177.INFECT	496	1.0000	2.0000	1.9940	.77614 -1
6178.ARTHRITI	496	1.0000	2.0000	1.9940	.77614 -1
6179.DIABET	499	1.0000	2.0000	1.9158	.27792
6180.NUTRIT	496	1.0000	2.0000	1.9940	.77614 -1

Electrodiagnostic Evaluation

VARIABLE	N	MIN	MAX	MEAN	STD DEV
7001.HEIGHT	386	56.000	77.000	69.957	2.7589
7002.WEIGHT	386	103.00	320.00	181.88	28.011
7007.SURALAMP	388	0.	23.800	8.7575	4.4099
7008.SURALDL	372	2.8000	5.3000	3.6839	.35836
7009.TIBAMP	386	.20000	20.500	8.7223	3.7725
7010.TIBDL	386	3.0000	6.1000	4.4433	.58276
7011.TIBPA	386	.70000	-116.200	6.5289	2.9367
7012.TIBCV	386	30.000	67.000	43.997	4.4104
7013.MEDSAMP	385	0.	41.000	17.625	6.7700
7014.MEDSDL	385	2.7000	6.4000	3.4582	.43228
7015.MEDSPA	379	0.	26.000	7.7335	3.3403
7016.MEDSCV	379	42.000	69.000	55.430	4.7983
7017.ULNSAMP	385	2.0000	35.000	14.748	5.9857
7018.ULNSDL	385	2.8000	4.4000	3.3997	.31087
7019.ULNSPA	376	.90000	50.000	7.0939	3.5990
7020.ULNSCV	376	40.000	70.000	57.473	5.3888
7021.ULNMAMP	386	2.6000	15.800	10.214	1.9173
7022.ULNMDL	386	2.2000	4.8000	2.7839	.30263
7023.ULNMPA	386	2.2000	15.000	9.1917	1.9027
7024.ULNMCV	386	43.000	74.000	57.474	4.6827
7025.POLYNEUR	386	1.0000	3.0000	1.7098	.80824
7026.MONONEUR	386	1.0000	3.0000	1.2798	.50909
7027.MOTORABN	386	0.	5.0000	.45078	.76203
7028.SENSEABN	386	0.	9.0000	2.1218	2.1009
7029.MTAMPLL	386	21.000	583.00	229.58	70.921
7030.MTAMPNM	386	11.000	143.00	79.096	19.494
7031.MTCVLL	386	87.000	136.00	111.74	8.1919
7032.MTCVNM	386	74.000	115.00	94.751	6.9406
7033.MTTMCVLL	386	90.000	163.00	132.50	12.271
7034.MTTMCVNM	386	67.000	121.00	98.619	9.0538
7035.SNAMPLL	386	13.000	296.00	126.80	45.270
7036.SNAMPNM	386	6.0000	115.00	49.756	17.600
7037.SNCVLL	386	0.	124.00	105.48	11.451
7038.SNCVNM	386	0.	110.00	93.142	10.132
7039.SNTMCVLL	386	82.000	122.00	106.86	6.3934
7040.SNTMCVNM	386	64.000	110.00	91.904	7.6551

Quantitative Tremor Test

VARIABLE	N	MIN	MAX	MEAN	STD DEV
8031.ACCRMS	490	.31400	3.8360	.85109	.41417
8032.ACCAVAMP	490	.24000	3.4270	.66483	.34054
8034.DSRMS	490	.18900	2.3390	.90794	.30368
8035.DSAVEAMP	490	.11600	1.9010	.66898	.24705

Urinary Measures

VARIABLE	N	MIN	MAX	MEAN	STD DEV
9001.PROTEIN	501	.10000	162.60	8.0882	12.725
9002.CREAT	501	15.000	352.80	117.56	54.982
9003.ALBUMIN	501	.10000	58.800	2.1766	5.6832
9004.BNAG	501	0.	90.000	1.8843	5.9097
9005.UMERCURY	501	1.0000	79.000	6.1399	8.4825
9016.LGPROCRE	501	-.32634	3.3629	1.6909	.35878
9017.LGALBCRE	501	-.32634	3.2509	1.0155	.41460
9018.LGBNAGCR	486	-1.3263	1.9097	-.26355 -1	.41953
9019.LGUHGCRE	485	-.32838	1.8407	.60594	.37932

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