Published in final edited form as:

Crit Rev Toxicol. 2017 November ; 47(10): 845–866. doi:10.1080/10408444.2017.1342599.

Persistence of mercury-induced motor and sensory neurotoxicity: systematic review of workers remotely exposed to mercury vapor

Cheryl A. Fields*,

Department of Environmental Health Sciences, Yale School of Public Health, New Haven, Connecticut, USA

Jonathan Borak, and

Departments of Medicine and Epidemiology & Public Health, Yale School of Medicine, New Haven, Connecticut, USA

Elan D. Louis

Department of Neurology, Yale School of Medicine, and Department of Chronic Disease Epidemiology, Yale School of Public Health, New Haven, Connecticut, USA

Abstract

Background—Elemental mercury (Hg^0) is a well-recognized neurotoxicant, but it is uncertain whether and for how long its neurotoxicity persists. Among studies that evaluated *previously-exposed* workers, only one examined workers during and also years after exposure had ceased.

Objective—To create a series of ‘synthetic’ longitudinal studies to address the question of persistence of Hg^0 neurotoxicity in occupationally exposed workers.

Methods—We systematically reviewed studies describing objective motor and sensory effects in *previously-exposed* mercury workers. Data from physical examination (PE), neurobehavioral (NB) tests and electrophysiological studies were extracted into structured tables and examined for their consistency and dose-relatedness and then compared with the corresponding results from studies of currently-exposed workers.

Results—We identified six cohorts that described neurological findings in 1299 workers, examined an average of 4.8 to 30 years after the cessation of exposure. Historical group mean U_{Hg} levels ranged from 23 to >500 $\mu\text{g/L}$, with U_{Hg} levels >6000 $\mu\text{g/L}$ in some individuals. Overall, few findings were significant; most were inconsistent across the remote-exposure studies, and in comparisons between studies of remotely- and currently-exposed workers.

Address for Correspondence: Cheryl Fields, Department of Environmental Health Sciences, Yale School of Public Health, New Haven, Connecticut, USA. Tel: 203-777-6611; cheryl.fields@yale.edu.

Declaration of interest: Jonathan Borak and Cheryl Fields are employees of Jonathan Borak & Company, which provides consulting services on environmental and occupational health issues (including concerns related to mercury exposure) to government and private clients. Both Ms. Fields and Dr. Borak are part time employees of Yale University. Elan Louis is a full-time employee of Yale University. The authors have not appeared in the last five years in any legal or regulatory proceedings related to the contents of this paper and have no plans to participate in such proceedings in the future. Dr. Borak and Ms. Fields contributed to the research reported in this paper during their normal course of employment without supplementary funding or external support.

Conclusion—The results of this systematic review indicate that Hg⁰-related neurotoxic effects detectable on PE, NB testing, and EPS are substantially reversed over time. To the extent that such effects do persist, they are reported principally in workers who have had very high dose exposures. In addition, based on limited available data, those effects reported to persist have been described as having little or no functional significance.

Keywords

occupational disease; elemental mercury; persistence; neurotoxicity; tremor; physical examination; neurobehavioral function; motor function; electrophysiological studies

Introduction

The neurotoxicity associated with long-term occupational exposure to elemental mercury vapor (Hg⁰) has been well described (International Programme on Chemical Safety 2003; World Health Organization 1991). Less certain is whether and for how long objective findings of toxicity persist following cessation of exposure. Some case reports describe the persistence of neurological abnormalities (White et al. 1993; Cordeiro, Jr. et al. 2003), while others indicate that such toxic effects may be transient (Bidstrup et al. 1951; Vroom and Greer 1972; Wood et al. 1973; Adams et al. 1983; Florentine and Sanfilippo 1991). Reversal of neurotoxicity has been documented even in workers following massive exposures (e.g. 24-hour urine mercury levels of 1495-7950 µg) (Bidstrup et al. 1951).

One explanation for this uncertainty is the general lack of longitudinal studies evaluating the neurological function of mercury-exposed workers during exposure and then years following exposure cessation. We are aware of only one study that evaluated neurological effects longitudinally in workers during active exposure and then again years after exposure cessation. But that study, which only included workers with relatively low exposure levels not expected to cause objective changes, found no significant differences on neurobehavioral tests between workers and controls for either time period (Ellingsen et al. 2001; Bast-Pettersen et al. 2005). Thus it provides no insights regarding persistence.

There also exist a small number of studies that described only the results of neurological examinations of mercury-exposed workers performed years *after* the cessation of their exposures (i.e. 'previous-exposure') of which some also described the workers' historical levels of Hg⁰ exposure. They reported sometimes significant, but seemingly inconsistent findings and, as a group, they have not been the subject of critical review or comparison. Moreover, because none of these studies evaluated the neurological status of the study workers while they were being actively exposed, it is uncertain whether the reported findings represented a change from the workers' neurological status during active exposure.

Lacking informationally-useful longitudinal studies on the persistence of Hg⁰ toxicity, we created a series of 'synthetic' longitudinal studies to address the question of persistence. In the first step, we performed a systematic literature review to identify studies that described neurological findings in groups of workers during on-going Hg⁰ exposure (i.e. 'currently-exposed' workers). We then documented the type and frequencies of objective neurological effects reported in those studies, stratified according to their group mean U_{Hg} into four

exposure categories. We presumed that the most consistently reported effects that also displayed a dose-related pattern across studies were more likely to be the consequence of Hg exposure, and as such they could provide a first approximation of the neurological effects that one would have expected in the previously-exposed workers had they been examined during active exposure to comparable levels of Hg⁰. The findings of that review are presented in a companion article (Fields et al. in press).

In the second step, we summarized the types, frequencies, and dose-relatedness of neurological findings reported in the previous-exposure studies and compared them to the corresponding findings reported in studies of currently-exposed workers with Hg⁰ exposure levels similar to those documented historically. Differences or similarities in the prevalence of specific neurological findings between the previously- and currently-exposed workers could thus serve as an indirect measure of the persistence or change in dose-related neurotoxic effects following exposure cessation.

The present report describes the methods and findings of that 'second step'.

Methods

Identification and selection of studies

A comprehensive literature search was performed to identify studies that evaluated neurological effects in workers after their exposure to elemental mercury had ceased. Studies were located by searching MEDLINE (1950 – December 15, 2015) using multiple search terms: neurotoxicity or toxicity or health effects; and elemental mercury or mercury vapor or occupational exposure to mercury vapor. We also examined international and government agency reports and reviewed reference lists from identified studies to ensure that all relevant studies were included in this review (details of our search methods are presented in Fields et al. (in press)). We considered studies published in English, French, German, Italian, Portuguese, and Japanese languages. Included for analysis were peer-reviewed cohort studies that described: 1) workers that had been occupationally exposed to Hg⁰ vapor, but not other forms of mercury, generally for at least 3 months; 2) the level of Hg⁰ exposure documented by measurements of mercury in urine, blood, or workplace air; 3) neurological effects involving motor function and/or sensory function; 4) testing methods and objective neurological findings from evaluations performed at least one year after exposure to mercury had ceased. Information from non-peer-reviewed publications was considered if it pertained to an eligible study. We did not consider neurological effects related to memory and cognitive function, as these findings were the subject of a meta-analysis (Meyer-Baron et al. 2002) and systematic review (Meyer-Baron et al. 2004).

Our analysis focused on objective effects that could be measured using validated methods; subjective symptoms were not included. In addition, some study authors qualified their findings as either 'clinical' or 'subclinical'. Unless otherwise stated, we assumed these terms were used in accordance with the following definition: '*Subclinical* toxicity refers to exposure-induced adverse effects that are too small to produce signs and symptoms evident in a standard clinical examination' (National Research Council 1992). Null findings were

those that were not statistically significant or were paradoxical (i.e. yielded findings that suggested mercury exposure improved performance).

Data extraction

Objective motor and sensory effects described in studies were extracted and tabulated into three categories reflecting the general types of evaluations used to examine workers: Physical Examination (PE); Neurobehavioral tests (NB); and Electrophysiological Studies (EPS). The PE category included mainly qualitative findings from clinical neurological examination; the NB category included results from functional performance tests that yield quantitative measures of tremor, motor and sensory functions, color vision, and balance; and the EPS category included quantitative findings from nerve conduction studies, electromyography, evoked potentials and electroencephalography. To permit comparisons across studies, examination findings and test results were further organized by domain (e.g. motor vs. sensory), and then, when sufficient details were provided, according to specific test (e.g. nerve conduction), outcome evaluated (e.g. distal latency) and anatomic localization (e.g. median sensory nerve).

Studies used a variety of NB functional performance tests to evaluate motor skills other than steadiness (used to detect tremor). Tests included those that assess only motor skills (i.e. dexterity, motor speed and grip strength) and those that assess motor ability as well as other abilities such as correct perception/information processing (i.e. perceptual motor speed, attention and reaction time). Because the latter set of tests does not provide information exclusively about motor function, we analysed those results (referred to as 'motor accuracy') separately from the results of tests that assessed only motor skills (referred to as 'motor function') (Goldstein and Sanders 2004).

We summarized the results reported for '*exposure effects*' (i.e. comparisons between exposed vs. controls) separately from results reported for '*dose effects*' (i.e. the dose-response associations between neurological findings and differing levels or patterns of exposure).

We stratified cohorts into exposure categories according to group mean urine mercury (U_{Hg}) levels determined during the period of active exposure, expressed as $\mu\text{g/L}$. The results of our analyses are stratified into the following four categories of exposure:

High	$U_{Hg} \geq 200 \mu\text{g/L}$;
Medium	$100 \mu\text{g/L} < U_{Hg} < 200 \mu\text{g/L}$;
Low	$50 \mu\text{g/L} < U_{Hg} < 100 \mu\text{g/L}$;
<BEI	$U_{Hg} < 35 \mu\text{g/g creatinine} \approx < 50 \mu\text{g/L}$.

The final category ('<BEI') refers to the Biological Exposure Index, a health-based guideline recommended by the American Conference of Governmental Industrial Hygienists that 'generally indicates the concentration below which nearly all workers should not experience adverse health effects' (American Conference of Governmental Industrial Hygienists (ACGIH) 2012). Prior to 2014, the era that included even the most recent of the reviewed studies, the BEI for elemental mercury was $35 \mu\text{g/g creatinine}$ (ACGIH 2013 ACGIH 2014).

Results

Studies and study populations

We identified 13 published studies from four countries that evaluated neurological effects in nine separate cohorts of workers with historical exposure to mercury vapor (He et al. 1984; Albers et al. 1988; Moriwaka et al. 1991; Bluhm et al. 1992; Andersen et al. 1993; Ellingsen et al. 1993; Kishi et al. 1993, 1994; Mathiesen et al. 1999; Letz et al. 2000; Powell 2000; Frumkin et al. 2001; Bast-Pettersen et al. 2005). Three of the 13 studies were excluded from further analysis, one because it described workers who had suffered only acute (16-hour) accidental exposure (Bluhm et al. 1992), another because it had no control group and provided few methodological details (He et al. 1984), and the third because workers had also been exposed to organic Hg (Powell 2000). Thus, our analysis was limited to 10 studies that evaluated motor and sensory neurological effects in six cohorts that met our criteria; findings were described in a total of 1299 mostly male workers (675 historically-exposed workers and 624 non-exposed controls). Only one study (Frumkin et al. 2001) included females (<10% of the original study population), but the actual number that participated in neurological evaluations was not stated. Table 1 presents the descriptive characteristics of these previous-exposure cohorts. There were three cohorts in the High Exposure category, and one each in the <BEI-, Low-, and Medium Exposure categories.

Bast-Pettersen et al. (2005), the <BEI Exposure cohort, performed NB testing in 49 workers at a Norwegian chloralkali facility and 49 age-matched male controls employed in a cellulose facility. Exposed and control workers were comparable with regard to education, lifestyle factors, shift work and previous concussions. Exposure to mercury had ceased 4.8 years (range: 4.2-10.0) before testing. Many of the study subjects (41 exposed, 40 controls) had also been examined about five years earlier (during the period of Hg exposure); at that time, Ellingsen et al. (2001) found no significant differences between exposed and control workers' performance on any of the NB measures of dexterity, speed, attention, and reaction time.

Inclusion/Exclusion Criteria: Male workers employed for at least 1 year; workers whose exposures had ceased more than 10 years prior to the examinations were not included. Exposed and control workers were excluded for 'alcohol abuse, major head injuries, metabolic, major psychiatric or neurological disease causing severe disability'.

Dose assessment: Individual dose assessments were based on U_{Hg} measurements obtained quarterly starting in 1949. Urines were adjusted for creatinine concentration after 1981; samples collected before 1982 were adjusted using the mean of individual creatinine measured in 1982 and 1983. For quarters without U_{Hg} data, each worker's levels were estimated using the mean of U_{Hg} measurements collected before and after the missing quarter. These quarterly data were used to calculate the mean U_{Hg} for each year. Exposures for each worker were characterized as cumulative U_{Hg} (sum of all mean annual U_{Hg} levels) and mean exposure intensity (cumulative U_{Hg} /years of exposure).

Dose-response assessment: The study authors did not evaluate the dose-relatedness of effects in previously-exposed workers, however, multiple linear regression analyses (MLR) were used to evaluate correlations between NB outcomes and exposure status (yes/no) in analyses that included the following covariates: age, shift work, alcohol consumption, smoking or snuffing, history of head injury with loss of consciousness (LOC), medication, and raw score of WAIS Information Test. In addition, they compared the differences between each individual's test scores determined while they were actively exposed and their test scores determined five years after exposures had ceased.

Frumkin et al. (2001), **the Low Exposure cohort**, performed PE, NB testing, and EPS in 139 US chloralkali workers and 107 age-, sex-, and race-matched community controls; after exclusion criteria were applied, the actual number of workers tested varied across each type of evaluation. Exposures had ceased 5.7 years (range: 0-35) before testing. Twenty-six workers had continued to work at the site for 3 years following its closure, but their 'exposure was felt to be negligible'.

Inclusion/Exclusion Criteria: Workers were employed for at least 1 year between 1956 and 1994. Exposed and controls with renal failure or acute intoxication (EtOH, drugs) were excluded from all analyses. Additional exclusions from specific peripheral or central nervous system testing were made on a case-by-case basis for the following: use of anticonvulsant or major psychiatric medications; alcoholism; illicit drug use; head trauma with LOC; familial tremor or Parkinson's disease; or a history of stroke, psychosis, cancer chemotherapy, renal disease, trauma to tested limb, or vestibular disease.

Exposure assessment: Individual exposures from 1956-1994 were reconstructed using a job-exposure matrix (JEM) that incorporated direct-read area air samples data obtained by plant personnel ('about 25,000' samples over 488 separate days between 1967 and 1993), and 48 personal samples obtained over 15 days in 1988, 1990 and 1992 by OSHA, NIOSH, and Duke University researchers (Williams et al. 2001). However, for 20 of the 38 study years there were no air Hg data; instead, exposure data for those years were 'interpolated from the earlier and later years based on employee account of factory conditions...' (Williams et al. 2001, p.82). Exposures were characterized in terms of mean exposure (2-106 $\mu\text{g}/\text{m}^3$), cumulative exposure (1.9-904.7 $\mu\text{g}/\text{m}^3$ -years) and peak (also referred to as 'maximum') exposure (7-147 $\mu\text{g}/\text{m}^3$).

The JEM air estimates were validated using 590 urine samples obtained from 78 workers by plant personnel during November 1988 - May 1991. Spearman correlation coefficients between the reconstructed air levels and levels estimated from the urinary data were statistically significant for all three metrics (mean exposure: $r=0.52$; cumulative exposure: $r=0.69$; and, peak exposure: $r=0.74$). Notably, those were the only U_{Hg} measurements that were deemed 'complete and of relatively high quality' from more than three decades of facility operation. The mean U_{Hg} was 72.4 $\mu\text{g}/\text{L}$ (13.0-191.5). Based on those data, this cohort was categorized as Low Exposure. However, there is evidence that those U_{Hg} levels likely underestimated workers' exposures. First, a NIOSH survey of the plant (Reh et al. 1991), which measured U_{Hg} in 89% (58 of 65) exposed workers in April, 1988, reported that mean U_{Hg} was 136 $\mu\text{g}/\text{g}$ creatinine (range 2-689), roughly equivalent to 190 $\mu\text{g}/\text{L}$ (range:

3-965). Among the 24 of 58 workers (41%) who worked in the cell room, mean U_{Hg} was 281 $\mu\text{g/g}$ creatinine, roughly equivalent to 393 $\mu\text{g/L}$. And, as described in Williams et al. (2001), Hg^0 air levels peaked in 1987 and then declined during 1988-91; cell room Air_{Hg} during those three years were 24-45% lower than in the years immediately before and after.

Dose-response assessment: Frumkin et al. (2001) used stepwise multiple linear regressions (or logistic regression for dichotomized variables) that included ‘appropriate covariates’ to evaluate ‘exposure effects’ and ‘dose effects’ for each of three continuous air Hg exposure measures: mean exposure, cumulative exposure, and peak exposure. All such analyses of PNS and CNS outcomes included the following covariates: age, ‘other mercury exposures’, ‘other neurotoxins’, fillings, and an index of cumulative alcohol consumption. Additional covariates specific to analyses of PNS outcomes included gender, height, body mass index (BMI), limb temperature), while the covariates for CNS outcomes included race, education, visual contrast sensitivity score, vocabulary score, WRAT-R reading score, and current use of sedative medications.

The Ellingsen Medium Exposure cohort, was described in three related studies (Andersen et al. 1993; Ellingsen et al. 1993; Mathiesen et al. 1999) that reported PE, NB testing, and EPS in 77 former workers at a Norwegian chloralkali facility following its closure and 53 age-matched male controls employed at a fertilizer factory. Two workers and one control declined NB testing. Exposed workers and controls were similar with regard to ‘socioeconomic background’ and ‘lifestyle habits’ (Andersen et al. 1993, p. 431). Exposures had ceased on average 12.3 years before testing.

Inclusion/Exclusion Criteria: Male workers, less than 65 years old at the time of examination, exposed for at least 1 year between 1947 and 1987, with U_{Hg} levels measured during at least four 3-monthly periods of employment. Exclusion criteria included a history of alcohol abuse, ‘major head injuries’, ‘metabolic disorders’, neurological, psychiatric or other diseases causing ‘severe disability’, and exposure to other known occupational neurotoxicants above ‘specified levels’ (Mathiesen et al. 1999).

Exposure/dose assessment: Individual dose assessments were based on more than 2300 urine Hg measurements obtained quarterly between 1948 and 1987. For each worker, doses were characterized for cumulative U_{Hg} (sum of annual mean urine levels), mean exposure intensity (cumulative U_{Hg} /years of exposure), and duration (in years). Direct-read area samples for air Hg levels were measured between 1953 and 1987. These data, available as quarterly mean air levels, were used to calculate cumulative air levels (i.e. the sum of quarterly levels for each year). For the years without air Hg data (1947-1953), the calculated mean for 1954 was used.

Dose-response assessment: Dose-effects were evaluated after stratifying workers into ‘high’- and ‘low’-dose groups and then comparing findings in each of these groups with non-exposed controls. Five different stratification schemes were used in the analyses of outcomes on PE, NB testing, and EPS (the only dose metric evaluated in all three analyses was cumulative $U_{Hg} > 600 \mu\text{g/L}$). Group differences on PE outcomes were compared using chi-squared and Fisher's exact tests. Differences on NB outcomes were compared using

analysis of variance (ANOVA) and stepwise multiple linear regression analyses that included the following covariates: current alcohol consumption, age, vocabulary scores, head injuries and shift work. EPS outcomes were evaluated using Mann-Whitney tests, and stepwise multiple linear (or logistic) regression analyses that included age, and current levels of U_{Hg} and B_{Hg} in addition to historical dose/exposure metrics.

The Oak Ridge High Exposure cohorts—Former US mercury-exposed workers at the US Oak Ridge lithium production facility were the subject of PE, NB testing, and EPS performed on two separate occasions and described in two studies. The facility operated from 1953 to 1963 and was then dismantled (1965-66); ‘thus the greatest elemental mercury exposure took place from 1953 to 1966 with a much lower exposure subsequently’ (Kallenbach 1988, p.3).

Albers et al. (1988) described the initial evaluations, performed in 247 exposed workers, examined 21 years after exposure had ceased, and 255 non-exposed controls frequency-matched by 5-year birth intervals, retirement status, and final job title. The Albers et al. (1988) study summarizes the findings of a doctoral dissertation (Kallenbach 1988); that dissertation contains substantially more detailed exposure and effects data for these workers. Accordingly, the data in the Albers study and the Kallenbach dissertation have been combined (‘Albers cohort’).

Ten years later, Letz et al. (2000) evaluated 89 of the exposed and 83 of the non-exposed workers previously studied by Albers et al. (1988) plus an additional 33 subjects. Because the Letz study was not strictly a follow-up of the Albers study, we considered it a separate cohort (‘Letz cohort’). After exclusion criteria were applied, the remaining workers (79 exposed, 84 controls) were comparable in age, education, and income, although current alcohol consumption was higher in exposed workers (70.9%) than controls (60.7%). Workers were examined 30 or more years after exposure had ceased. A primary aim of the Letz study was to ‘replicate previous findings’ from the earlier (Albers et al. 1988) study, because that study had tested ‘a large number of associations between numerous exposure variables’, and ‘a number of the statistically significant associations...were not consistent across exposure measures’ (Letz et al. 2000, p. 460). A second objective was to better understand ‘age × exposure interactions’, i.e. whether ‘differences in neurologic dysfunction between exposure groups became larger with increasing age of the cohorts’ (Letz et al. 2000, p.460).

Inclusion/Exclusion criteria: Albers et al. (1988) identified workers employed at least 4 months between 1953 and 1966, and then selected those with the highest cumulative dose (≈12% of eligible exposed population). Letz et al. (2000) included those of the Albers subjects that were able to participate plus additional workers selected for historically high peaks >600 µg/L or cumulative exposure 2000 µg/L. Both Albers and Letz excluded acutely intoxicated (EtOH, drugs) subjects from all analyses (PE, NB testing, and EPS). Additional exclusions from specific peripheral or central nervous system testing were made on a case-by-case basis for the following: use of anticonvulsant or major psychiatric medications; alcoholism; illicit drug use; head trauma with LOC; diabetes; or a history of stroke, psychosis, cancer chemotherapy, renal disease, trauma to tested limb, or vestibular

disease. Albers reported results with ('restricted analysis') and without ('total group analysis') consideration of those exclusions; our analyses considered only Albers' 'restricted analysis'. Letz et al. (2000) reported results for only the restricted analysis and, in addition, excluded workers with 'mental retardation'.

Exposure/dose assessment: Individual dose assessments in both studies were based on U_{Hg} levels obtained on a quarterly basis from 1953-1986. For each worker, seven dose metrics were characterized: cumulative (sum of quarterly average U_{Hg} levels); duration (number of quarters with 'detectable' U_{Hg}); relative peak (worker's single highest U_{Hg} level); absolute peaks (number of quarters with at least one $U_{Hg} > 300 \mu g/L$; number of quarters with at least one $U_{Hg} > 600 \mu g/L$), average lifetime U_{Hg} level for 1953-1966; and the average U_{Hg} level for 1955-1956, 'the time period of greatest exposure'.

Dose-response assessment: Albers and Letz each evaluated associations between neurological outcomes and six dose metrics. The same five metrics were used in both cohorts, but each included a different metric for average U_{Hg} : Albers analyzed the average U_{Hg} level for 1955-1956, while Letz used the lifetime average U_{Hg} . Dose-relatedness was assessed for all of the outcomes evaluated in the Albers cohort, whereas Letz evaluated only a subset of seven 'primary' outcomes to minimize multiple comparisons.

The Hokkaido High Exposure cohort—Former Japanese mercury miners who had been 'severely exposed', many of whom had been hospitalized for mercury poisoning (the majority 5 or more times), were evaluated in a series of overlapping studies an average of 18 years after the mine's closure in 1970. Objective neurological findings from PE and NB tests were described in three studies. Moriwaka et al. (1991) described PE findings in 83 workers given 'neurological examinations'. Two subsequent studies (Kishi et al. 1993, 1994) described the methods and results of NB testing in 117 workers. In the first of those, Kishi et al. (1993) reported 'exposure effects' based on a matched-pair analysis limited to exposed workers 'with a history of mercury intoxication' ($n=76$) and an equal number of controls individually matched by age (± 3 years), sex, residence, and education. In the second, Kishi et al. (1994) described the correlations between various dose metrics and NB test scores from analyses that included the 76 historically intoxicated workers and 41 workers 'without mercury intoxication'. The study authors did not provide an explanation for the differing numbers of workers examined in these reports.

Inclusion/exclusion criteria: Inclusion criteria were not explicitly stated; however Kishi (1993, 1994) noted that all examined workers were male. Exclusion criteria were not discussed.

Exposure/dose assessment: Kishi and Moriwaka relied upon historical exposure data published in two earlier studies from the same mine that had evaluated workers during active exposure. The Hashiba (1954) report provides longitudinal exposure and health effects data from 1950 through 1951 for workers monitored by 'regular health examinations and urine mercury analyses once a month' (Kishi et al. 1993, p. 294). The Suwa report (Suwa & Takahata 1969) provides cross sectional data (PE and U_{Hg} levels) from workers examined before the closure of the mine. Workers had been exposed to air levels that were 'usually

over 1000 $\mu\text{g}/\text{m}^3$, and historical U_{Hg} in miners diagnosed with mercury poisoning ranged from 500 to >2000 $\mu\text{g}/\text{L}$ in 95% of cases (Kishi et al. 1993, 1994).

Dose-response assessment: Kishi et al. (1994) used stepwise MLR that controlled for ‘potential confounding factors’ (i.e. age, education, frequency of alcohol intake, and current working status) to evaluate correlations between NB test scores and ‘dose effects’ for each of three exposure measures: duration of exposure, job exposure categories, and history of intoxication. Job exposure categories were ‘classified by the exposure to mercury based on the data by Hashiba’ (Kishi et al. 1994, p. 38); ‘mining, refining, and transporting jobs showed higher percentages of having a past history of mercury poisoning’ than maintenance and clerical jobs (Kishi et al. 1993, p. 294). As detailed in Hashiba (1954), 70.2-81.5% of workers in mining, refining and transportation jobs were diagnosed with Hg poisoning (range by job type: 58.3-92.9%), in contrast to 12.5-13.5% of workers in maintenance and clerical jobs. MLR analyses that included the ‘product of the subject’s age and the presence or absence of a history of mercury intoxication’ were also used to investigate ‘age $\times$ exposure’ interactions.

Neurological evaluations

The neurological findings described in the previous-exposure studies are presented below, grouped according to type of evaluation (PE, NB testing, and EPS).

Physical examination—PE was performed in five of the six previous-exposure cohorts; Bast-Pettersen et al. (2005) did not perform PE. Most of the studies performed comprehensive neurological PEs in exposed and control subjects with qualitative results mainly characterized as ‘normal’, ‘abnormal’ or ‘equivocal’. Semi-quantitative scales were used to judge strength (e.g. 0-5) and deep tendon reflexes (e.g. absent, diminished, normal, hyperactive). By contrast, Moriwaka et al. (1991) examined only formerly exposed workers and did not provide detailed examination methods.

All studies reported the percentage of workers with abnormal findings, but differed in the level of detail provided. Most described results for each test (e.g. finger-to-nose, patellar reflex) and/or functional domains (e.g. motor coordination, deep tendon reflexes), and some reported aggregated findings (e.g. abnormal PE). Differences in how studies tabulated results complicated direct comparisons between studies. One study reported only aggregated findings: Frumkin et al. (2001) considered a worker to have an abnormal PE if more than five findings were abnormal, and reported the percentage of subjects with such an abnormal PE. By contrast, Letz et al. (2000) defined an abnormal PE as having more than eight abnormal or equivocal findings. In the Ellingsen cohort, test results were not tabulated ‘if less than four exposed subjects and referents had pathological signs’ (Andersen et al. 1993).

With one exception (Moriwaka et al. 1991), studies used statistical analyses to determine whether the percentage of exposed workers with abnormal findings was significantly increased compared to controls and/or significantly correlated with exposure status (exposed vs. not exposed). Figure 1 presents summary results for seven outcomes on PE. Detailed results from specific tests and for dose-response analyses performed in each of the individual studies are presented in Supplemental Table 1.

Exposure effects: Comparisons between exposed and controls yielded few significant differences: reduced sensation was described in three studies, of which one also found evidence of reduced motor coordination (MC). Frumkin et al. (2001) found no significant difference in the percentage of exposed and control workers with abnormal examinations (8.9% vs. 4.1%, respectively); they did not indicate the types of abnormalities seen. In the Ellingsen cohort, differences were significant for two tests of 'reduced distal sensation' and for MC on tests of 'line walking' with eyes open, but not with eyes closed (Andersen et al. 1993). The authors noted that sensory loss 'due to a single peripheral nerve or root lesion' may have been related to a greater frequency of 'lumbar disc disease with sciatica' and 'nerve injury caused by accidents' in the exposed (Andersen et al. 1993, p. 432). Two of the three High Exposure cohorts also reported significantly reduced sensation. Letz et al. (2000) reported that a greater proportion of exposed workers had more than two abnormal or equivocal sensory findings, but did not provide further details. Albers et al. (1988) found significantly more errors on tests of joint position in the exposed, but noted that the finding of reduced distal sensation was 'complicated' by significant interactions with 'several baseline variables' (i.e. 'age and lead exposure') (Kallenbach 1988). In the Hokkaido cohort, Moriwaka et al. (1991) examined 83 exposed workers and reported the percentage with tremor (8.4%), 'ataxia' (1.2%), abnormal deep tendon reflexes (4.8%), and loss of sensation (3.6%). Because there were no controls, the significance of these findings cannot be determined. Notably, however, the percentage of exposed workers with abnormal findings was lower (2-9-fold) than that reported for corresponding tests in two groups of slightly older controls described in the other previous-exposure studies (Albers et al. 1988; Letz et al. 2000). Kishi et al. (1994) reported no significant differences on Romberg testing.

Dose effects: Dose effects were assessed in three cohorts. In the Ellingsen cohort, two approaches were used to evaluate dose effects. Andersen et al. (1993) compared the prevalence of effects between exposed workers, stratified into high- and low-dose groups, and controls. Significantly increased rates of reduced distal sensation, postural tremor, and impaired coordination were seen in workers (n=62) exposed above the cohort medians for duration (>70 months) plus annual U_{Hg} levels (>80.6 $\mu g/L$) compared to controls. A separate analysis stratified workers above or below the cumulative U_{Hg} level of 600 $\mu g/L$. Compared to controls, workers with cumulative U_{Hg} >600 $\mu g/L$ had significantly reduced distal sensation; workers with U_{Hg} levels <600 $\mu g/L$ did not differ significantly on any outcome.

In the second approach, Ellingsen et al. (1993) evaluated correlations between three historical measures of exposure and dose (cumulative U_{Hg} , cumulative Air_{Hg} , and duration of exposure), comparing results between workers with and without each of two PE findings, 'postural tremor/impaired coordination' and 'reduced distal sensation'. Using logistic regression analyses that included age, postural tremor/impaired coordination was significantly correlated with age and years since first exposure, whereas reduced distal sensation was significantly correlated with cumulative U_{Hg} and cumulative Air_{Hg} .

In the Albers cohort, dose effects were evaluated in three ways. First, MLR analyses were used to evaluate correlations between PE outcomes and highest-ever peak and/or cumulative urine mercury (Albers et al. 1988; Kallenbach 1988). 'Weak but significant' dose-response relationships ($r=0.09-0.13$) were found for four outcomes: postural tremor, finger-to-nose,

strength, and 'joint position' sensation. However, the results for tremor, finger-to-nose, and joint position were 'substantially influenced' by 'no more than 3 subjects'. When those outliers were excluded, the results were no longer significant.

Next, using logistic regression, subjects with one or more peak $U_{Hg} > 600 \mu\text{g/L}$ were compared to subjects without peak $U_{Hg} > 600 \mu\text{g/L}$ plus unexposed controls. Significant differences were seen for postural tremor, coordination, Babinski and snout reflexes, and strength. No information was provided regarding differences between the higher peak and lower peak workers (controls excluded) or between the lower peak workers and controls.

Lastly, historical measures of exposure and dose were compared for workers with and without postural tremor. As detailed in Kallenbach (1988), the restricted analysis showed that tremor had a borderline significant association with higher peak U_{Hg} (691 vs. 601 $\mu\text{g/L}$, $p=0.08$), but no significant associations were seen for the number of U_{Hg} peaks >300 or $>600 \mu\text{g/L}$, cumulative U_{Hg} , average U_{Hg} , or duration of exposure. A separate analysis considered the association between the neurologist rating of tremor and number of peak urines $>600 \mu\text{g/L}$. The proportion of workers with tremor increased as the number of such peaks increased: one (34%; 7/40), two (38%; 17/45), three (59%; 10/17), or four peaks (66%; 2/3). However, severity of tremor was not related to the number of U_{Hg} peaks $>600 \mu\text{g/L}$: all the cases of 'moderate' tremor were seen in those with none, one, or two peaks, while the subjects with three or more peaks had only 'trace' or 'mild' tremor.

In the Letz et al. (2000) cohort, dose-relatedness of PE findings was not evaluated.

In the Hokkaido cohort, Moriwaka et al. (1991) described the number of workers with PE abnormalities according to two groups: 31 workers who had been hospitalized for Hg poisoning and 52 'severely exposed' workers who had not been hospitalized. Tremor was more prevalent in the previously hospitalized workers (4/31 vs. 3/52). By contrast, loss of sensation and abnormal DTRs were seen only among workers who had never been hospitalized (3/52 and 4/52, respectively). Ataxia was only reported in one worker. Moriwaka did not report the workers' exposure levels, but the relative magnitude and differences in exposures between those two groups can be inferred as follows. According to Kishi et al. (1993), workers with a history of such hospitalization had spent more time in jobs within, rather than outside the mine. And, as documented in Hashiba (1954), average Hg levels inside the mine chute (1.5 mg/m^3 , range: 0.5-3.7) and pitface (2.7 mg/m^3 , range: 0.8-5.6) were much higher than those outside (0.9 mg/m^3 , range: 0.5-1.9).

Neurobehavioral testing—NB testing was performed in all six of the cohorts using a variety of quantitative tests to assess a range of neurological functions. Studies used statistical analyses to evaluate differences between exposed and non-exposed controls and to identify significant associations between test performance and historical measures of exposure and dose. Figure 2 presents summary results for six NB outcomes: tremor, motor function, motor accuracy, sensory function, color vision, and balance. Detailed results for specific tests and for dose-response analyses performed in individual studies are presented in Supplemental Table 2.

Studies reported the results for the individual tests performed, but the level of detail provided regarding specific test methods and results varied within and across studies. Some described the instruments used, their testing protocols and scoring criteria; others provided only the names of the test and reported test results without further detail. For example, tests of tremor and motor performance were performed in one or both hands. Some studies reported a single test score, either the average of the two hands or the 'preferred'/'dominant' hand. Others reported results for both hands separately: some reported results for 'dominant' and 'non-dominant' hands, while others reported for 'right' and 'left' hands. One study (Frumkin et al. 2001) did not describe its testing protocol, but provided the 'primary references to the particular methods used'. In our analyses, results of specific tests were tabulated as 'significant' if the study had reported a statistically significant difference in at least one of the tested hands.

NB tremor: NB testing of tremor was performed in all six cohorts. As detailed below, studies assessed tremor using *physiological techniques* that involve the use of sensors to measure specific tremor parameters (e.g. amplitude, frequency), and/or *hand-eye coordination tests* that measure motor steadiness.

Physiological tests of tremor: Four studies performed physiological tests of *postural tremor* by means of an accelerometer; three (Letz et al. 2000; Frumkin et al. 2001; Bast-Pettersen et al. 2005) used identical instruments (i.e. Catsys tremor pen). In addition to using an accelerometer, the fourth study (Albers et al. 1988) also evaluated *postural tremor* in formerly exposed workers using a force transducer.

Exposure effects: On accelerometry, tremor amplitude was significantly decreased in the Low Exposure cohort workers compared to controls (Frumkin et al. 2001), but no significant differences were found between exposed and controls in two High Exposure cohorts (Albers et al. 1988; Letz et al. 2000) or in the <BEI cohort (Bast-Pettersen et al. 2005). Tremor frequency was evaluated in two of the studies; no significant differences were observed (Albers et al. 1988; Bast-Pettersen et al. 2005).

On tests of *postural tremor* using a force transducer, Albers et al. (1988) found no significant differences between formerly exposed workers and controls for any of five parameters tested (data not shown). Two of those five null findings ('percentage of total power' and 'mean tremor frequency') had been the 'parameter most affected' (Kallenbach 1988) and 'the singularly most powerful result' in their studies of currently-exposed mercury workers (Miller et al. 1975; Langolf et al. 1978; Langolf et al. 1981).

Dose-effects: Three of the four studies evaluated the dose-relatedness of postural tremor measured using accelerometry. Two tested associations between one or more NB tremor parameters (e.g. amplitude, frequency, 'percentage of total power') and cumulative U_{Hg} and peak U_{Hg} (Albers et al. 1988; Letz et al. 2000), average U_{Hg} (Albers et al. 1988), and duration of exposure (Albers et al. 1988; Letz et al. 2000). Statistically significant dose-effects were found for only one tremor parameter, amplitude, which correlated significantly with duration of exposure in one study (Letz et al. 2000) and with several peak U_{Hg} metrics (i.e. highest ever peak, number of peaks >600 µg/L) in another (Albers et al. 1988). The

third study (Frumkin et al. 2001) found no association between amplitude and mean, cumulative or peak levels of Air_{Hg}.

Albers et al. (1988) found no evidence of dose-relatedness for *postural tremor* tested by force transducer in comparisons between subjects with one or more peak U_{Hg} >600 µg/L and those without such peaks (data not shown).

Hand-eye coordination tests of tremor: All six studies employed hand-eye coordination tests of motor steadiness. Five used computer-based tests: two used tests of static steadiness (Mathiesen et al. 1999; Bast-Pettersen et al. 2005), and four assessed tracking (Albers et al. 1988; Mathiesen et al. 1999; Letz et al. 2000; Frumkin et al. 2001). The sixth study (Kishi et al. 1993) used pencil and paper tests to assess tracking and aiming. Three used non-computerized tests that involved drawing of visually presented materials, i.e. Bender visual-motor gestalt test (BGT) (Kishi et al. 1993), and Benton visual retention test (B-VRT) (Mathiesen et al. 1999; Bast-Pettersen et al. 2005). The results of static steadiness, aiming, and tracking/drawing tests have been used to classify tremor respectively as postural, intention, or kinetic (Louis et al. 2000; Louis 2007; Buijink et al. 2012; National Institute of Neurological Disorders and Stroke 2012; Gonzalez-Usigli & Espay 2013; Sternberg et al. 2013).

Exposure effects: Tests of *postural tremor* were null in two studies (Mathiesen et al. 1999; Bast-Pettersen et al. 2005). One of those studies yielded paradoxical results: exposed workers performed significantly better on tests of static steadiness than controls (Bast-Pettersen et al. 2005). *Intention tremor* was assessed in one study: High Exposure cohort workers performed significantly worse on tests of aiming than controls (Kishi et al. 1993). *Kinetic tremor* was assessed in all six studies; significant results were reported in three. Mathiesen et al. (1999) found that Low Exposure cohort workers performed significantly worse than controls on tests of drawing (i.e. B-VRT), but did not differ on tests of tracking. Significant results were also found in two of the three High Exposure cohorts tested on tracking (Albers et al. 1988; Kishi et al. 1993).

Dose-effects: Five of the six studies evaluated the dose-relatedness of their findings; Bast-Pettersen et al. (2005) did not. No significant associations were seen between *postural tremor* and the highest tertiles of cumulative U_{Hg}, average U_{Hg}, or duration of exposure (Mathiesen et al. 1999). Kishi et al. (1994) found that *intention tremor* was significantly associated with job exposure categories and duration of exposure. All five cohorts examined the dose-relatedness of *kinetic tremor*; significant associations were found in all but the Low Exposure cohort. All three High Exposure cohorts found that poorer performance on tests of tracking was significantly associated with cumulative U_{Hg} (Albers et al. 1988; Letz et al. 2000), highest peak U_{Hg}, average U_{Hg}, and duration of exposure (Albers et al. 1988), and job exposure categories (Kishi et al. 1994). In the Medium Exposure cohort, Mathiesen et al. (1999) found no evidence of dose-relatedness for kinetic tremor assessed on tests of tracking, however, poorer performance on drawing tests was significantly associated with the highest tertiles of cumulative U_{Hg} (i.e. cumulative > 600 µg/L), average U_{Hg}, and duration of exposure. In the Low Exposure cohort, Frumkin et al. (2001) found no association between tests of tracking and mean, cumulative or peak levels of Air_{Hg}.

Motor function: Motor function (other than steadiness) was assessed in all six cohorts using tests of manual dexterity, motor speed, and grip strength.

Exposure effects: Manual dexterity was assessed in all six cohorts; significant results were found in three. Performance on Grooved Pegboard (or a similar instrument) was significantly worse in the Low Exposure cohort (Frumkin et al. 2001), the Medium Exposure cohort (Mathiesen et al. 1999) and one High Exposure cohort (Kishi et al. 1993) compared to controls. Mathiesen et al. (1999) noted that workers with deficits of dexterity were the same ones that had abnormal MC on PE: 'poorer performance on this test [grooved pegboard] among the exposed workers is in accordance with the observation of impaired coordination in the clinical neurological examination of the same workers.'

Motor speed was assessed in four cohorts using tests of finger tapping; significant results were reported in two. Significantly reduced motor speed was found in one Low Exposure cohort (Frumkin et al. 2001) and one High Exposure cohort (Kishi et al. 1993), but not in the other High Exposure cohort (Letz et al. 2000) or in the <BEI cohort (Bast-Pettersen et al. 2005).

Grip strength was assessed in four cohorts (3 High Exposure and 1 Low Exposure) using a hand dynamometer. Kishi et al. (1993) and Letz et al. (2000) evaluated both hands; Kishi reported scores for 'right' and 'left' hands separately, but Letz reported only a single test score. Albers et al. (1988) evaluated only the 'dominant' hand (Kallenbach 1988). Significant differences between exposed and controls were found in only one study: Kishi et al. (1993) reported significantly reduced grip strength in both hands of High Exposure cohort workers compared to matched controls.

Dose effects: Four of the six studies evaluated the dose-relatedness of manual dexterity and motor speed; all reported significant results in the expected direction. Deficits in manual dexterity were significantly associated with a variety of dose and exposure metrics in three studies (Albers et al. 1988; Mathiesen et al. 1999; Frumkin et al. 2001), but not the fourth (Kishi et al. 1994). Reduced motor speed was significantly associated with job exposure categories and exposure duration in a High Exposure cohort (Kishi et al. 1994), but showed no association with mean, cumulative or peak air Hg levels in the Low Exposure cohort (Frumkin et al. 2001). No evidence of dose-related grip strength was found in the three studies that assessed its dose-relatedness (Albers et al. 1988; Kishi et al. 1994; Frumkin et al. 2001).

Motor accuracy: Motor accuracy was assessed in all six cohorts using tests of attention and response speed (Simple Reaction Time (SRT), and Continuous Performance Tests (CPT)) and perceptual motor speed (Symbol Digit/Digit Symbol (SD)) (Johnson and Baker 1987).

Exposure effects: Significant results were reported in only one of the six studies that assessed attention and response speed. Kishi et al. (1993) found significantly slower SRT in High Exposure cohort workers compared to controls. By contrast, the remaining five studies found no significant differences for SRT. Findings were null in two studies that also tested CPT (Mathiesen et al. 1999; Bast-Pettersen et al. 2005).

Five studies assessed perceptual motor speed; no significant differences were found between formerly exposed workers and controls on SD tests. Kishi et al. (1993) did not perform SD testing.

Dose effects: The dose-relatedness of perceptual motor speed, attention and response time was evaluated in four of the six studies. Four assessed dose-relatedness of attention and response speed; significant results were reported in only one. Kishi et al. (1994) found slower SRT significantly associated with job exposure categories and duration of exposure. Only one of three studies found evidence of dose-relatedness of perceptual motor speed. In the Ellingsen cohort, Mathiesen et al. (1999) found that worse performance on Digit Symbol testing was significantly associated with only one of three dose/exposure metrics tested.

Balance: Balance was evaluated in three studies: two assessed postural sway (Letz et al. 2000; Frumkin et al. 2001); and one evaluated 'equilibrium duration' (Kishi et al. 1993).

Exposure effects: No significant differences were found between formerly exposed workers and controls.

Dose effects: Two of the three studies evaluated the dose-relatedness of balance; both reported null results. Poorer performance on tests of postural sway showed no association with mean, cumulative or peak levels of Air_{Hg} (Frumkin et al. 2001). Likewise, Kishi et al. (1994) found no significant associations between 'equilibrium duration' and job exposure categories or duration of exposure.

Sensory function: Sensory function (other than color vision) was quantitatively evaluated in three cohorts. Three studies measured vibrotactile thresholds (of fingers and great toe) using vibrometers; two (Frumkin et al. 2001; Letz et al. 2000) used identical instruments.

Exposure effects: Frumkin et al. (2001) found that Low Exposure cohort workers performed significantly worse than controls for both upper and lower limbs. By contrast, studies of two High Exposure cohorts found no significant differences in vibrotactile thresholds between exposed workers and controls (Albers et al. 1988; Letz et al. 2000). Albers et al. (1988) also found no significant differences on tests of two-point discrimination or touch-pressure.

Dose effects: Two of the three studies evaluated the dose-relatedness of their sensory findings. Frumkin et al. (2001) found no association between vibrotactile thresholds and mean, cumulative or peak levels of Air_{Hg}. Albers et al. (1988) reported inconsistent findings for quantitative testing of two-point discrimination (significant dose-response for hands (p=0.04) but not feet (p=0.65)), touch-pressure (significant dose-response for feet (p=0.01) but not hands (p=0.33)), and vibrotactile threshold (significant dose-response for feet (p=0.01) but not hands (p=0.33)).

Color vision: Color vision was evaluated in one cohort; Frumkin et al. (2001) found no statistically significant differences between exposed workers and controls evaluated using the Color Confusion Index (CCI).

Dose effects: Frumkin et al. (2001) found no significant dose-relatedness between poorer performance on CCI and mean, cumulative or peak levels of AirHg.

Electrophysiological testing—EPS, using electromyography and surface electrodes, were performed in four of the six cohorts. In all four, nerve conduction studies (NCS) were used to evaluate responses to electrical stimulation of peripheral nerves. One cohort was also examined using evoked potentials (EPs) to evaluate the electrical activity of the central nervous system. In the Ellingsen (Andersen et al. 1993) and Albers (Kallenbach 1988) cohorts, NCS testing was performed on the ‘right’ side of the body; Frumkin et al. (2001) and Letz et al. (2000) did not specify such details. In the Ellingsen cohort, Andersen et al. (1993) performed bilateral testing of EPs and reported results separately for the ‘right’ and ‘left’ side outcomes. Statistical analyses were used to evaluate differences between exposed and non-exposed controls and to identify significant associations between test performance and historical measures of exposure and dose. All studies analyzed differences between group mean values of test results, while one study (Andersen et al. 1993) also reported the number of individuals with pathological findings on NCS (i.e. >2 standard deviations (SD) from mean values of control group) or EPs (i.e. >3 SDs from mean values of control group). Figure 3 presents summary results for NCS and visual evoked potentials (VEPs). Detailed results for specific tests and for dose-response analyses performed in individual studies are available in Supplemental Table 3.

Nerve conduction studies: NCS were performed in four studies that each assessed a variety of motor and/or sensory functions in up to five different nerves and up to four different parameters, yielding 25 unique combinations (e.g. ‘ulnar sensory latency’); results were reported for a total of 49 outcomes. Nerve conduction velocity (NCV) and amplitude were the most frequently evaluated parameters (15 outcomes each), followed by distal latency (11 outcomes) and F-wave latency (8 outcomes).

Exposure effects: Comparisons of exposed workers and controls revealed only one significant abnormality in the expected direction. In High Exposure cohort workers, Letz et al. (2000) reported a statistically significant slowing of ulnar motor NCV, while slowing of peroneal motor NCV approached significance ($0.05 < p < 0.10$). In the other High Exposure cohort, Albers et al. (1988) found no group differences using a Mann-Whitney U test or by analysis of covariance that included age, height, weight, finger volume, and a history of lead exposure.

By contrast, the remaining two cohorts found paradoxically faster NCV in exposed workers. Frumkin et al. (2001) found that exposed workers had significantly faster NCV than controls for peroneal motor NCV ($p < 0.02$) and for a composite measure of NCV that included ulnar motor NCV ($p < 0.03$). Andersen et al. (1993) also found that exposed workers had faster NCV in three of four nerves tested, but these results were not statistically significant. In addition, they found a non-significant increase in the proportion of controls with ‘pathological’ deficits on three of six NCS outcomes as compared to the exposed workers.

Dose-effects: All studies that performed NCS also assessed the dose-relatedness of their findings. Of 25 unique outcomes (e.g. median sensory NCV) evaluated in one or more studies, seven were significantly associated with historical urine and/or air Hg metrics. However, only one (ulnar motor NCV) was significantly dose-related in more than one study.

Frumkin et al. (2001) found a significant association between slowing of proximal ulnar motor NCV and cumulative Air_{Hg}, while slowing of distal ulnar sensory NCV was significantly associated with estimates of cumulative and peak Air_{Hg}, but not average Air_{Hg}.

In the Ellingsen cohort, the dose-relatedness of NCS was evaluated using two approaches. In one, Andersen et al. (1993) tested the associations between 14 NCS outcomes and two categorical measures of exposure/dose. Workers with cumulative U_{Hg} >600 µg/L had statistically significantly slower median nerve NCV (motor and sensory) compared to controls, but no other differences were seen. Workers with peak U_{Hg} >300 µg/L showed no significant differences from controls on any of the 14 NCS outcomes tested. In the other, Ellingsen et al. (1993) evaluated correlations between eight selected NCS outcomes and three continuous measures of historical exposure/dose (cumulative U_{Hg}, cumulative Air_{Hg}, number of peak U_{Hg} >200 µg/L) using MLR analyses that included age and current U_{Hg} and B_{Hg} levels. Two NCS outcomes were significantly correlated with one or more measures of exposure/dose: sural sensory amplitude with cumulative U_{Hg} and peak U_{Hg} >200 µg/L, and median sensory NCV with cumulative Air_{Hg}.

MLR analyses were also used to evaluate the influence of current consumption of alcohol or smoking on NCS outcomes. Slowing of median motor nerve NCV was significantly associated with increasing consumption of alcohol (p=0.02), while smoking had no effect on NCS outcomes.

In the Albers et al. (1988) cohort, dose effects were evaluated in two ways. First, MLR analyses were used to assess correlations between 14 NCS outcomes and two historical dose metrics. A significant association was seen between median sensory latency and highest peak U_{Hg}, but not cumulative U_{Hg}. Highest peak U_{Hg} was also significantly correlated with the 'total number' of motor nerve abnormalities. Next, using analysis of covariance, workers with peak U_{Hg} >600 µg/L had significantly prolonged median sensory latency and borderline slowing of ulnar motor NCV compared to those without such peaks plus unexposed controls. Comparisons of workers with two or more U_{Hg} peaks >600 µg/L vs. all other subjects found significant increases in the total number of abnormalities in motor (p=0.005) and sensory (p=0.04) nerves.

In the Letz et al. (2000) cohort, MLR analyses were performed to evaluate correlations between three 'selected' NCS outcomes (ulnar and peroneal motor NCV, and peroneal F-wave latency) and three historical dose/exposure metrics. Slowing of ulnar motor NCV was significantly correlated with higher levels of cumulative U_{Hg}, peak U_{Hg}, and increasing exposure duration. Prolonged F-wave latency in the peroneal nerve was significantly correlated with higher cumulative U_{Hg} and approached significance for peak U_{Hg}.

($0.05 < p < 0.10$). Associations between peroneal NCV and exposure approached significance for cumulative and peak U_{Hg} ($0.05 < p < 0.10$).

Evoked potentials: EP responses (visual [VEP], brainstem [BEP] and somatosensory [SEP]) were studied in only the Medium Exposure cohort (Andersen et al. 1993).

Exposure effects: No significant differences were seen for either VEP (n=10 results) or BEP (n=8 results) between exposed workers and controls, while one of 10 SEP results was paradoxically better in the exposed. There were ‘few subjects’ with pathological findings (details not provided).

Dose-effects: The dose-relatedness of EPs was evaluated using two approaches. In one, Andersen et al. (1993) evaluated the relationship between all three types of EP responses and exposure intensity. Of 56 comparisons performed (i.e. 28 EP results for each of two dose metrics), significant differences between controls and exposed workers were seen for only three: workers with peak $U_{Hg} > 300 \mu\text{g/L}$ had significantly prolonged N75 latency in VEP bilaterally, while workers with cumulative $U_{Hg} > 600 \mu\text{g/L}$ had significantly reduced distal NCV in SEP unilaterally. No significant differences were seen for BEP responses.

In the other approach, Ellingsen et al. (1993) evaluated correlations between four VEP responses (latency and amplitude, bilaterally) and three dose/exposure metrics (cumulative air Hg , cumulative U_{Hg} , and the number of U_{Hg} peaks $> 200 \mu\text{g/L}$). Of twelve possible correlations, only one, the association between prolonged N75 latency in the right eye and the number of peak $U_{Hg} > 200 \mu\text{g/L}$, was statistically significant.

Peripheral neuropathy

Exposure effects: The relationship between mercury exposure and ‘peripheral neuropathy’ (PN) or ‘polyneuropathy’ was evaluated in four of the cohorts. In the Low Exposure cohort, Frumkin et al. (2001) ‘found little evidence of peripheral neuropathy’; their diagnostic criteria were not described. In the Medium Exposure cohort, Andersen et al. (1993) defined ‘polyneuropathy’ as symmetrically decreased deep tendon reflexes in the legs plus reduced distal limb sensation and/or muscular wasting with distal paresis; by that definition, none of the subjects had polyneuropathy.

In one of the High Exposure cohorts, Albers et al. (1988) evaluated subjects for ‘polyneuropathy’ on PE, but diagnostic criteria were not described. Paradoxically, the prevalence of clinical polyneuropathy was higher in non-exposed controls than in exposed subjects: 7.8% vs. 5.5%, respectively (Kallenbach 1988).

In the other High Exposure cohort, Letz et al. (2000) proposed four alternative criteria for ‘peripheral neuropathy’ based on combinations of nerve conduction and functional test abnormalities (e.g. proprioception of the great toe, Achilles tendon reflex, vibrotactile threshold, and sway speed). PN was significantly correlated with exposure status (i.e. ‘exposed vs. unexposed’), however prevalence rates of PN were not reported.

Dose effects: Based on PE, Albers et al. (1988) categorized exposed workers as ‘normal’, ‘equivocal’, or ‘polyneuropathy’ (criteria not described) and further stratified them based on peak U_{Hg} levels: <450 $\mu g/L$; 450-699 $\mu g/L$; 700-850 $\mu g/L$; and >850 $\mu g/L$. Using MLR analyses that adjusted for potential confounding factors including age, diabetes mellitus, and ‘reported drinking problems’, the prevalence of polyneuropathy was significantly increased only in workers with peaks >850 $\mu g/L$.

A separate analysis compared historical dose metrics in exposed workers with and without PE evidence of polyneuropathy. Workers with ‘clinical polyneuropathy’ had significantly higher peak U_{Hg} levels than normal subjects (885 $\mu g/L$ vs. 600 $\mu g/L$), but no significant differences were found for other dose/exposure metrics (i.e. number of U_{Hg} peaks >300 or >600 $\mu g/L$, average U_{Hg} , and exposure duration) (Kallenbach 1988).

Letz et al. (2000), using stepwise regression that controlled for age, found that associations of PN with cumulative U_{Hg} approached significance ($0.05 < p < 0.10$), while highest peak U_{Hg} and exposure duration were not significantly associated.

Age-by-exposure interactions—Interactions between mercury exposure and age were examined in four of the six previous-exposure cohorts; significant results were found in two High Exposure studies.

In the Albers cohort (Albers et al. 1988; Kallenbach 1988) age-by-exposure interactions were evaluated for selected outcomes. Significant interactions between age and cumulative U_{Hg} were reported for six outcomes: proximal and distal strength on PE, tremor amplitude (assessed two ways), and quantitative measures of touch-pressure sensation (foot) and vibration sensation (foot). Significant interactions between age and highest peak U_{Hg} for those six outcomes plus three others (two-point discrimination in hand and foot, and motor nerve abnormalities) were also seen. No evidence of age-by-exposure interactions was found on analyses of several other outcomes including polyneuropathy on PE, sensory nerve abnormalities, and NB tests of tracking, dexterity, or reaction time.

Kishi et al. (1994) evaluated interactions between age and ‘a history of mercury intoxication’ on NB outcomes. Significant findings were reported for aiming (left, but not right hand) and manual dexterity, but no such interactions were found on tests of tracking, reaction time, or motor speed (tapping). Likewise no interactions were found for quantitative tests of balance and grip strength.

Age-by-exposure interactions were not found in two other studies. Letz et al. (2000) found no such interaction for tremor amplitude, or for any of the other ‘primary outcomes’ evaluated: peroneal motor NCV; peroneal motor F-wave latency; ulnar motor NCV; hand-eye coordination (i.e. tests of tracking); and diagnosis of peripheral neuropathy. Likewise, Bast-Pettersen et al. (2005) found no evidence of an interaction between age and exposure based on comparisons of NB test scores in workers tested during active exposure and then retested five years after exposure cessation. During the interval between evaluations, performance on several NB tests of motor function decreased significantly in both exposed and control workers, but the magnitude of change in test scores was similar in both groups.

Comparison of neurological findings in current- vs. previous-exposure studies: In this section, we compare the neurological findings reported in the previous-exposure studies with those findings in current-exposure studies that were reported most consistently and also showed evidence of dose-relatedness, as described in the systematic review by Fields et al. (in press). Results are presented below for each type of neurological evaluation (PE, NB testing, and EPS).

Physical examination

In the studies of currently-exposed workers, a variety of abnormal neurological findings were reported. Most were seen almost exclusively in High Exposure studies. Tremor, impaired MC, and abnormal DTRs were reported most frequently, described in 78%, 39%, and 50% of the High Exposure studies, respectively. Evidence of dose-relatedness was seen for each. Impaired sensation was described less often (22% of the High Exposure studies), but also demonstrated dose-relatedness.

By contrast, none of the five previous-exposure cohorts evaluated on PE had statistically significant increases in tremor or abnormal DTRs in comparisons of exposed workers and controls, and only one showed a significant increase in impaired MC. Reduced sensation, found in three of the five cohorts, was the only significant effect reported with consistency among the previous-exposure cohorts. However, the meaning of that finding is unclear. As previously described, in two of those cohorts (Albers, Ellingsen), the findings of reduced distal sensation were ‘complicated’ by associations with factors unrelated to mercury exposure. Moreover, Ellingsen et al. (1993) also noted that findings of ‘slightly reduced distal sensation’ were not associated with tremor, the most widely recognized neurological effect of mercury exposure. Accordingly, the association between reduced sensation and previous exposure to mercury remains uncertain. Table 2 contrasts the PE findings in the previous-exposure studies and the corresponding findings reported in current-exposure studies with similar exposure levels that evaluated those functions.

On the other hand, the absence of increased tremor, impaired MC and abnormal DTRs in direct comparisons of exposed and control groups in the previously-exposed studies, even among the High Exposure cohorts, is not surprising. Results from our analyses in currently-exposed workers indicated that the point prevalence rates for each of these findings did not exceed the corresponding rates found in controls until group mean U_{Hg} levels were >275 $\mu\text{g/L}$. As such, we would expect to find significant increases in the prevalence of these PE abnormalities only among subgroups of the most highly exposed workers, as was seen on the dose-related analyses performed in three previous-exposure cohorts (Ellingsen, Albers, and Hokkaido). Significant increases related to exposure status (i.e. exposed vs. controls) would only have been expected in the Hokkaido cohort, where historical group mean U_{Hg} was >500 $\mu\text{g/L}$. However, the point prevalence in the former Hokkaido miners was much lower than the corresponding prevalence averaged across studies of currently-exposed workers with similar U_{Hg} levels (i.e. 500 $\mu\text{g/L}$) for tremor (8.4% vs. 42.3%), abnormal MC (1.2% vs. 28.5%), and abnormal DTRs (4.8% vs. 35.8%). It is particularly striking that the point prevalence in those previously-exposed workers was 5- to 24-fold lower than in the currently-exposed workers who were on average 20 years younger, because neurological

findings are expected to be more prevalent as age increases. Such findings support the likelihood that the abnormalities improved after removal from exposure.

Taken together, the data from the current- and previous-exposure studies provide little evidence that clinically detectable neurological effects of mercury vapor exposure persist following cessation of exposure.

Neurobehavioral testing

In the studies of currently-exposed workers, the most consistently reported NB outcomes were tremor, poorer performance on tests of dexterity and motor speed, and normal results on tests of perceptual motor speed, attention or reaction time. Dose-relatedness was also seen for NB tremor (all types combined, and for postural and kinetic tremors, but not intention tremor) and for dexterity and motor speed.

A similar pattern of NB outcomes was seen in studies of previously-exposed workers. However, as shown in Table 3 and discussed below, differences between studies of currently- and previously-exposed workers were seen for some of the specific outcomes.

NB tremor—The studies of currently- and previously-exposed workers both found significant evidence of NB tremor in comparisons of exposure status, but seemingly contradictory differences were seen with respect to the types of tremor observed. In the current-exposure studies, evidence was strongest for postural tremor (11 of 17 studies had significant findings), mixed for intention tremor (4/7), and weakest for kinetic tremor (1/7). By contrast, in the previous-exposure studies, evidence was strongest for kinetic tremor (3/6) and weakest for postural tremor (1/5).

To better understand these differences, we also considered the dose-relatedness of tremor types using three approaches. First, we examined the proportion of studies with significant tremor findings across increasing categories of exposure. Next, we examined the group mean U_{Hg} levels in studies with significant vs. null findings for tremor. Lastly, we considered data from those individual studies that analyzed dose-response. Summary results of these analyses are presented in Table 3 for all tremor combined ('overall') and for each tremor type.

Postural Tremor: A sufficiency of data for postural tremor in the current-exposure studies provided clear dose-relatedness across increasing categories of exposure (Table 3). In addition, the U_{Hg} data for postural tremor in current-exposure studies showed strong evidence of dose-relatedness: the weighted average of group mean U_{Hg} in studies with significant findings was nearly 5-fold higher than that of studies with null results (184 vs. 39 $\mu\text{g/L}$). Lastly, twelve of the 17 current-exposure studies which evaluated postural tremor also assessed its dose-relatedness. Significant results, found in half of those studies, were seen more frequently with higher exposure: 75% of the four High Exposure cohorts, 50% of the two Medium and 50% of the two Low Exposure cohorts, but only 25% of the four <BEI (Miller et al. 1975; Langolf et al. 1978; Roels et al. 1982; Fawer et al. 1983; Verberk et al. 1986; McCullough et al. 2001).

In contrast to the strong evidence of dose-related postural tremor across studies of currently-exposed workers, no consistent evidence of dose-relatedness was seen in the previous-exposure studies (Table 3). The results of dose-response analyses performed in individual studies (n=4) were only significant in the High Exposure cohorts, but the associations with specific dose metrics differed between those two cohorts (as detailed in Supplemental Table 2). Taken together, these data suggest that postural tremor (as detected on NB testing) may persist in highly exposed workers (e.g. those with peak $U_{Hg} > 600 \mu g/L$), but would not be expected to persist in workers with lower exposure.

Kinetic tremor: The number of studies that evaluated kinetic tremor was limited; however evidence for its dose-relatedness was seen in both current- and previous-exposure studies and across all three approaches used to evaluate dose-relatedness (Table 3). Three of the four (75%) current-exposure studies that performed dose-response analyses reported that deficits on tests of drawing or tracking were dose-related (Camerino et al. 1981; Langworth et al. 1992; Ellingsen et al. 2001). The findings of kinetic tremor in three of six previous-exposure studies and its apparent dose-relatedness in current- and previous-exposure studies support the possibility that kinetic tremor, as detected on NB testing, can persist following cessation of mercury exposure. These data also suggest that kinetic tremor should not be expected to persist in cohorts of workers with group mean $U_{Hg} < 100 \mu g/L$. It is possible that observations based on so few studies are due to chance, but the consistency of the findings argues against that possibility.

Intention Tremor: The data for intention tremor are less clear. No evidence of dose-related intention tremor was found among the current-exposure studies, including the four studies that performed individual dose-response analyses in five groups of workers (Roels et al. 1982; Roels et al. 1989; Gunther et al. 1996; Wastensson et al. 2006) (Table 3). The only previous-exposure study that evaluated intention tremor found evidence of its dose-relatedness in a High Exposure cohort. Overall, the limited data available for intention tremor from the previous- and current-exposure studies neither support nor discount the possibility that intention tremor, as detected by NB testing, is a persistent effect of mercury exposure.

Motor function—Studies of both currently- and previously-exposed workers found significantly poorer performance on tests of dexterity and motor speed in exposed workers compared to controls (Table 3). These deficits showed consistent evidence of dose-relatedness in the individual dose-response analyses performed in the Medium and High Exposure studies, but only inconsistent evidence in the Low Exposure studies. Overall, these data suggest that deficits in dexterity and motor speed, as detected by NB testing, may persist in some workers with high historical Hg exposures (e.g. peak $U_{Hg} > 300 \mu g/L$).

Motor accuracy—Compared to controls, performance on tests of perceptual motor speed, attention or reaction time was normal in all studies of currently-exposed workers and in all but one of the previous-exposure studies. In the most highly exposed previous-exposure cohort, significant deficits were reported only in reaction time, deficits that were not dose-related (Kishi et al. 1994). Likewise, no dose-relatedness was found for reaction time in

studies of three other previous-exposure cohorts (Albers, Frumkin, Ellingsen). Among ten current-exposure studies that evaluated dose-response, significant results were limited to two: one Low Exposure study that reported significantly slowed reaction time in a subgroup of workers (Camerino et al. 1981), and one <BEI study that reported a significant positive correlation between duration of exposure and only one of two tests of reaction time (Liang et al. 1993) (as detailed in Fields et al., in press).

The sufficiency of data for testing of motor accuracy in the current- and previous-exposure studies (i.e. 38 outcomes tested: 25 tests of attention and response speed; 13 tests of perceptual motor speed) and the lack of significant findings support the conclusion that exposure to elemental Hg is unlikely to adversely affect motor accuracy (i.e. tests which require motor ability as well as other abilities such as correct perception/information processing).

Section summary—Overall, results of NB testing in current- and previous-exposure studies provide strong evidence for the reversal of postural tremor. On the other hand, the data raise the possibility that kinetic tremor and poorer performance on tests of dexterity and motor speed may persist.

Electrophysiological studies

Nerve conduction studies—NCS were performed in the High, Medium, and Low Exposure cohorts of currently- and previously-exposed workers. The proportions of current- and previous-exposure cohorts tested by NCS were identical across those exposure categories.

Despite such similarities in testing, as shown in Table 4, there were striking differences seen in the frequencies of statistically significant NCS outcomes documented in the current-exposure studies (24%; 17 of 72 outcomes) vs. the previous-exposure studies (4%; 2 of 49 outcomes).

Only one of the two significant findings in previously-exposed workers was in the expected direction. That finding, slowing of ulnar motor NCV, was reported in only one of two High Exposure cohorts tested. The meaningfulness of that particular finding is uncertain, given that no significant differences in ulnar motor NCV were found in the seven studies of currently-exposed workers (Vroom and Greer 1972; Zedda et al. 1980; Angotzi et al. 1981; Albers et al. 1982; Levine et al. 1982; Triebig & Schaller 1982; Urban et al. 1999), including four that were in the High Exposure category.

The other significant finding in previously-exposed workers, a paradoxical one of significantly faster peroneal motor NCV in the Low Exposure cohort (Frumkin et al. 2001), directly contrasts with the findings of slower peroneal motor NCV seen in High Exposure cohorts of previously- (Letz et al. 2000) and currently-exposed workers (Gilioli et al. 1976; Albers et al. 1982).

Overall, the inconsistency of the specific NCS findings and the more than 10-fold decrease in the overall frequency of statistically significant findings in previously-exposed workers provides evidence that mercury-related NCS abnormalities are not persistent.

Evoked potentials—Current-exposure studies found statistically significant differences between exposed workers and controls for VEPs, but not BEPs or SEPs. Significant differences on VEP testing were found only for latency (on 5 of 6 outcomes tested) but not for amplitude (1 of 9 outcomes). By contrast, the only previous-exposure study that evaluated EPs, a Medium Exposure cohort, found no statistically significant differences between workers and controls on tests of VEP, BEP or SEP (Ellingsen et al. 1993).

Section summary—Overall, results of EPS in current- and previous-exposure studies provide no evidence for the persistence of electrophysiological abnormalities.

Discussion

Our systematic review looked for evidence of persistent neurological effects among workers with a broad range of Hg^0 exposures who were examined on average 4.8 to 30 years after the cessation of exposure. Historical average U_{Hg} levels exceeded currently recommended limits in all but one of the six ‘previous-exposure’ cohorts, and peak U_{Hg} levels 600 $\mu\text{g/L}$ were documented in 16% to 45% of the workers in the Medium and High Exposure cohorts, respectively. Some workers had U_{Hg} levels that were extraordinarily high ($>3000 \mu\text{g/L}$). For perspective, the U_{Hg} level currently recommended by the ACGIH as a biological exposure limit for healthy workers exposed 40 hours/week for 6 months or longer is 20 $\mu\text{g/g}$ creatinine, equivalent to about 28 $\mu\text{g/L}$ (ACGIH 2013). Thus some of the study subjects had U_{Hg} levels approximately 20- to 100-fold higher than currently recommended levels.

Despite such exposures, there were few consistent significant findings, seen almost exclusively among the most highly exposed workers. Comparisons of objective neurological outcomes between studies of previously- and currently-exposed workers suggest that deficits on NB tests of tremor, dexterity, and motor speed were most likely to persist, particularly in subsets of highly exposed workers. PE findings of postural tremor and impaired MC may also persist in such workers. In some cases, impaired sensation also seemed to persist. The paucity of neurological effects following previous mercury exposure contrasts with the effects associated with current or recent exposure and lends support to the more general view that ‘exposure-related neurological dysfunction is often reversible, and only rarely is the toxic exposure so massive ... that irreversible neuronal changes ensue’ (Schaumburg & Spencer 1987; Albers et al. 1988). As discussed below, that possibility is supported by epidemiological data that document the reversibility of Hg^0 -related neurological effects.

Reversibility of effects

Substantial improvement or complete normalization of PE abnormalities has been documented in studies that performed follow-up examinations in selected workers after their removal from exposure. Vroom & Greer (1972) examined nine of the ‘most severely affected’ workers from an untold number of symptomatic employees of a US thermometer factory. Those nine workers had a mean U_{Hg} of 1320 $\mu\text{g}/24 \text{ hrs}$ and abnormal PE findings

that included 'severe' tremor (n=9), abnormal DTRs (n=2), and 'broad-based gait' (n=1). Motor signs were so severe in six of the nine that 'eating, drinking, and dressing were performed with great difficulty and two ... had virtually stopped walking because of unsteadiness'. Improvement in motor function was characterized as 'good' to 'excellent' after removal from exposure (17-20 months) in eight workers, most of whom had also been treated with the heavy metal chelating agent, British Anti-Lewisite (n=7), and 'poor' in one worker followed only 13 months, and noted to have had 'the most severe over-all deficit'. That last worker had recovered from the 'overt' motor signs and tremor, but was judged 'poor' based on his performance on tests of tapping.

Gonzalez-Fernandez et al. (1984) examined five workers employed 5 to 7 years in a small workplace that manufactured Hg relays; mean U_{Hg} levels averaged 446 $\mu\text{g/L}$ and ranged up to 1100 $\mu\text{g/L}$ during the 10 months prior to PE. Tremor and abnormal MC were seen in all five workers and nystagmus in four. Removal from exposure (2 months) and chelation treatment (multiple oral doses of N-acetyl-DL-penicillamine) was associated with 'rapid improvement' of motor signs in all five workers.

Normalization of PE findings has also been observed in workers removed from exposure who did not receive chelation treatment. Chaffin et al. (1973) and Miller et al. (1975) performed follow-up examinations in 12 workers four to six months after cessation of exposure. Workers were selected on the basis of having the highest blood and/or urine mercury levels during the initial assessment of 32 chloralkali workers. Five of the 12 had cerebellar abnormalities (i.e. intention tremor and/or dysdiadochokinesia). Normalization of cerebellar signs was seen in four workers with an initial group mean U_{Hg} of 426 $\mu\text{g/L}$ (range: 205-670) and retest mean U_{Hg} of 65 $\mu\text{g/L}$ (range: 32 -108), but persisted in the fifth worker who had higher U_{Hg} levels (initial: 790 $\mu\text{g/L}$, retest: 412 $\mu\text{g/L}$).

Bidstrup et al. (1951) performed follow-up evaluations of five workers employed for years in the repair of direct-current meters who had been diagnosed with 'chronic mercury poisoning'. Four of the five had 'coarse irregular tremors' that resolved in three within a year of removal from exposure. At the time of diagnosis, the three had 24-hr U_{Hg} levels of 1495-3900 μg . Tremor persisted in the fourth worker whose initial 24-hr U_{Hg} level was 7950 μg , and who had been re-exposed to mercury. The fifth worker complained of intermittent tremor, but tremor was not documented on examination. Figure 4 illustrates the improvement documented 12 months after exposure cessation in Bidstrup's case 1, whose initial 24-hr U_{Hg} was 1495 μg .

Improvement of abnormal DTRs and impaired sensation has also been documented. Adams et al. (1983) described a worker who developed hyperactive DTRs, intention tremor, fasciculations, and reduced vibratory sensation after spending two days salvaging liquid Hg from industrial grade thermometers. Urine Hg, first collected 3 ½ months after the exposure incident, was 98.75 $\mu\text{g/L}$. On follow-up examination performed about 5 ½ months after the exposure incident, his neurological findings 'were completely normal'.

Follow-up data in the Chaffin et al. (1973) and Miller et al. (1975) and Bidstrup et al. (1951) studies document a similar pattern of improvement. Persistent effects were rare, and only

observed in workers who had very high U_{Hg} levels. By contrast, most Hg^0 -related PE abnormalities resolved following removal from exposure. Although these findings were based on small numbers of observations, and might have been due to chance, similar results were reported in the largest study that assessed neurological effects in previously-exposed workers. In that study, Albers et al. (1988) compared PE findings of tremor in 228 exposed workers and 236 controls. No significant increase in tremor prevalence was seen in the previously-exposed workers overall, but tremor prevalence was significantly increased in those with one or more peak $U_{Hg} > 600 \mu g/L$; the proportion with persistent tremor increased as the number of samples with $U_{Hg} > 600$ increased.

Significant improvements in performance on NB tests of postural tremor, dexterity, and tapping have also been documented in studies that performed follow-up testing in selected workers after exposure was reduced or stopped. Miller et al. (1975) reported statistically significant improvements on tests of dexterity in 32 workers retested 4-6 months after exposure was reduced from a mean U_{Hg} of 599 to 292 $\mu g/L$. In addition, motor speed in 11 workers was significantly improved 4-6 months after removal from exposure (mean U_{Hg} levels fell from 596 to 95 $\mu g/L$). Similarly, Langolf et al. (1978) documented improved tapping scores in four of five workers retested 6-10 months after removal from exposure (mean U_{Hg} fell from 660 to 200 $\mu g/L$). Both studies also reported significant improvements in postural tremor on follow-up testing of subsets of workers, based on changes in tremor parameters measured using physiological techniques.

Functional significance of persistent effects—Given that some mercury-related neurological effects may persist long after exposure cessation, we sought to understand the functional significance of those PE effects most likely to be the consequence of Hg exposure (i.e. tremor impaired MC, and DTRs). Only two of the previous-exposure cohorts, Albers and Ellingsen, provided perspective on this question. They were the only cohorts with statistically significant, persistent PE findings of tremor (in high-dose workers only) and impaired MC. Both studies also reported significantly reduced sensation on PE, and significant deficits on NB tests of tremor and manual dexterity.

In the Albers cohort, Kallenbach (1988) observed that ‘many of the measures examined indicate decreasing performance but not necessarily of impairment’. That distinction was not defined or further discussed. In the Ellingsen cohort, Andersen et al. (1993) concluded that abnormalities on PE were ‘slight’ and ‘in nearly all cases cannot be classified as disease’. They specifically observed that ‘postural tremor did in most cases not interfere with the subjects [*sic*] daily activities’.

Similar observations were noted in the current-exposure studies. As detailed in Fields et al. (in press), five of the six studies that explicitly commented on the clinical and/or functional significance of their findings (from among the 46 studies that performed PE) described ‘minor’ or ‘mild’ findings that were ‘clinically insignificant’. Among these were two High Exposure studies that specifically noted the absence of functionally significant effects (Chaffin et al. 1973; Langolf et al. 1978). The only current-exposure study that described functionally significant abnormalities on PE was one that had ‘selected’ workers based on the severity of their symptoms (Vroom et al. 1972).

Together, these limited observations provide perspective on the reversibility of mercury-related abnormalities, but they do not rule out the possibility of residual, functionally-significant deficits. However, as persistent, statistically significant, dose-related PE findings of tremor and impaired MC were reported only in the Ellingsen and Albers cohorts, it seems likely that functionally significant findings would be seen only following very high doses and peak exposures. Accordingly, we next considered the exposure/dose levels most closely associated with persistent effects.

Exposure/dose levels associated with persistent effects—Although none of the previous-exposure studies found statistically significant increases in tremor prevalence on PE in comparisons between exposed workers and controls, dose-related increases were seen in subsets of highly-exposed workers in three cohorts (Albers, Hokkaido and Ellingsen). The dose levels reported for those three cohorts suggest that PE tremor persisted only in workers with peak U_{Hg} levels $\geq 500 \mu g/L$. In the Albers cohort, the critical dose measure associated with persistent postural tremor was peak $U_{Hg} > 600 \mu g/L$. In the Hokkaido cohort, tremor increased two-fold in workers with ‘mercury poisoning’, of whom 95% had $U_{Hg} > 500 \mu g/L$ (with a range up to $> 2000 \mu g/L$). In the Ellingsen cohort, the dose-relatedness with peak U_{Hg} is less clear: Ellingsen et al. (1993) documented postural tremor in 14 of 77 workers and peak U_{Hg} levels $> 600 \mu g/L$ in 12 of 77 workers. Although they did not specifically discuss the association between tremor and peak U_{Hg} , they did note that their findings were ‘in agreement with’ Albers, who reported ‘increased prevalence of tremor ... among the highest exposed subjects’ (Ellingsen et al. 1993, p. 743). PE findings of impaired coordination and reduced sensation showed similar dose-related effects in the Albers and Ellingsen cohorts.

The dose levels associated with deficits on NB tests of tremor, dexterity, and motor speed were also similar to those seen for PE abnormalities. In the Albers cohort, poorer performance on tests of postural tremor and dexterity were attributed to historical peak $U_{Hg} > 600 \mu g/L$: ‘a residual effect of the higher mercury exposure in the 1950’s ... those who had at least one mercury urine value above $0.6 mg/L$ ’ (Kallenbach et al). In the Hokkaido cohort, increased prevalence of deficits on NB tests of intention tremor, kinetic tremor, and motor speed were seen in workers with the highest levels of exposure (e.g. $U_{Hg} \geq 500 \mu g/L$). In the Ellingsen cohort, deficits on NB tests of kinetic tremor and dexterity were significantly associated with cumulative $U_{Hg} > 600 \mu g/L$, and average $U_{Hg} > 110 \mu g/L$ (Mathiesen et al. 1999). It is notable that peak U_{Hg} levels were $> 600 \mu g/L$ in 12 and $> 300 \mu g/L$ in 28 of 77 workers, but associations between peak U_{Hg} levels and NB test results were not reported. However, workers with peak $U_{Hg} > 300 \mu g/L$ comprised 69% (18 of 28) of the workers with cumulative $U_{Hg} > 600 \mu g/L$ (Andersen et al. 1993). Similar dose-relatedness between quantitative tests of sensation and peak $U_{Hg} > 600 \mu g/L$ was seen in the Albers cohort.

Two other cohorts reported dose-relatedness for NB tremor (Letz cohort) and tests of dexterity (Frumkin cohort), but did not indicate the specific levels associated with persistent effects.

Section summary—The reported findings of reversibility and dose-response indicate that residual neurological effects, particularly persistent tremor and impaired coordination on PE, can be found mainly in subsets of the most heavily exposed workers, particularly after very

high peak exposures. That finding is consistent with Kallenbach's conclusions about the Albers cohort: 'With reference to the large majority of the 222 exposed workers that were studied, there is no evidence to suggest that there were 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' (Kallenbach 1988, p. 187).

The possibility of persistent NB effects after less extreme exposures is suggested by findings in the Ellingsen and Frumkin cohorts, although neither provided sufficient exposure data to affirm that possibility, and their findings of persistence were inconsistent with results reported for the High Dose cohorts of Albers and Letz. It seems contrary to expectations that persistent effects would be manifested in lower dose, but not higher dose cohorts.

One possible explanation for such inconsistency involves the adequacy of the exposure and dose-response assessments as described in those two cohorts. A sizeable proportion of the Ellingsen workers had peak exposures that were very high; it is tempting to attribute the observed deficits to such exposures. Unfortunately, the available data do not allow us to test that hypothesis. As for the Frumkin study, it is likely that workers' exposures were underestimated. As described above, exposures were estimated using a JEM based on air levels obtained during three years when exposure levels were unusually low. In addition, a NIOSH plant survey during the time studied by Frumkin reported a mean U_{Hg} level nearly three-fold greater than that reported by Frumkin; 41% of the workers had mean U_{Hg} levels $>600 \mu\text{g/g}$ creatinine (Reh et al. 1991). Thus we cautiously propose that the results of the Ellingsen and Frumkin cohorts also support the view that effects persist only following very high peak exposures.

Age-by-exposure interaction

The possibility of an interaction between age and exposure level was initially raised by Albers et al. (1988) and Kallenbach (1988). They proposed that aging, which reduces the capacity of compensatory mechanisms, might unmask prior subclinical neurotoxic damage in some individuals as a 'consequence of age-related neuronal attrition' (Albers et al. 1988, p. 659). They also suggested that their hypothesis that manifestations of Hg^0 -induced neurotoxicity might be delayed until aging supervened 'could be tested in a longitudinal study ... if the aging/unmasking hypothesis is true, then then exposure group over subsequent years should show an increased incidence of abnormal tremor compared to the control group' (Kallenbach 1988, p. 182).

We are aware of only two previous-exposure studies that provide such longitudinal perspectives. Letz et al. (2000), a follow-up study of the Albers cohort, found that 'contrary to the results of the previous investigation, no age by exposure interaction was observed in the current study'. In the second study, Bast-Pettersen et al. (2005) found no evidence of age-exposure interactions in $<BEI$ Exposure workers who underwent NB testing during active exposure and then five years after exposure ceased. If there were a positive age-by-exposure interaction, it would more likely have been seen in the High Exposure than $<BEI$ workers; among the latter, abnormal effects were neither expected nor observed. Accordingly, the very limited empirical data provides no evidence that Hg^0 -related neurotoxicity is unmasked by aging, but additional studies are necessary to clarify this issue.

Implications of these results

The findings of our analysis have potentially important implications for the clinical assessment and care of formerly-exposed mercury workers and others with persistent or late-onset neurological deficits. It is our experience that historical Hg⁰ exposure is often listed prominently among the likely disease etiologies for such patients, especially those who initially present with postural tremor or impaired MC on PE. While such an association is possible, it seems increasingly unlikely the more distant in time and less extreme the level of exposure. The risk of too readily ascribing such residual effects to previous Hg⁰ exposure is that more likely and potentially more treatable causes of impairment may be ignored. Accordingly, consideration of historical Hg⁰ exposures as the cause of persistent neurological impairment requires that the nature and intensity of exposure be documented as carefully as possible. In the absence of a history of prolonged or extreme Hg⁰ exposures, other causes of neurological dysfunction should be rigorously pursued. Individual evaluations should be performed on a case-by-case basis considering individual factors, exposure history and medical history. Because the findings of this review derived predominantly from group-level data, their extrapolation to the clinical care of individuals should be made with caution.

Likewise, there is no evidence that Hg⁰-related neurotoxicity manifests itself only later in life after exposure has ended. To the contrary, our review indicates that following exposure cessation, such neurotoxicity improves or normalizes over time. Thus the onset of neurological deficits years after removal from exposure should not be readily attributed to Hg⁰ exposure. Such attributions can also lead to the failure to diagnose more likely, treatable conditions.

Limitations of this systematic review

The main limitation of the present review is the lack of longitudinal studies that could directly inform whether Hg⁰-related neurological effects are persistent. Lacking such studies we constructed synthetic longitudinal studies, using reports of effects in currently-exposed workers to approximate the clinical status that probably would have been observed in the previously-exposed workers if they had been evaluated during exposure. However, that approach is limited by deficiencies of the current-exposure literature. As we have noted elsewhere (Fields et al., in press), those limitations include the failure of several of the older studies to describe detailed findings, use specific tests consistently, include matched controls, or perform statistical evaluations.

It also seemed possible that limitations of study quality among the previous-exposure studies might have influenced the findings in the present review. We did not assign these studies to quality tiers, as we had done in our previous review (Fields et al., in press), because the small number of studies under consideration precluded the usefulness of such an approach. Instead, for each of the studies, we described in detail their use of control groups, inclusion/exclusion criteria, and analytical methods used to minimize confounding (Methods section), and provided a transparent way to interpret the meaningfulness of the PE results of the Hokkaido cohort (Results section). We believe that this approach transparently provides the same information, but with even greater detail than using the summary tiers. However, had

we assigned quality tiers, each of these studies would have been in the highest tier (tier 1) except for the Hokkaido cohort, which would have received a tier 1 rating for NB, but a tier 3 rating for PE due to the lack of a control group. Accordingly, we see no basis to suggest that limited study quality affected our present results.

We considered the possibility that the apparent dearth of persistent effects was due to the use of inappropriate control groups in the previous-exposure studies. However, as described in the Methods section, all of those studies had matched controls to exposed workers by age and gender, and noted their comparability with regard to education. In addition, most had excluded workers with other known or suspected confounders and/or adjusted for their impact using statistical models.

Moreover, in the Ellingsen cohort, study authors noted ‘a possible selection towards healthier referents’ because controls had been selected ‘among current employees’ whereas 9% of the exposed workers were not actively working at the time of the study (Andersen et al. 1993, p. 431). In the Hokkaido cohort, Kishi also noted that ‘a higher percentage of referents were currently working than exmercury miners, mainly because many of the referents over 60 years old were farmers’ (Kishi et al. 1993, p. 294). That difference is a likely explanation for the finding of significantly weaker grip strength in exposed workers compared to controls; in a dose-response analysis, stronger grip strength was significantly associated with ‘working or not working’, but not with any of the metrics of mercury exposure. As the selection of ‘healthier’ control groups would have biased results away from the null, we find no evidence to suggest that the lack of abnormal findings on PE in previously-exposed workers could be due to inappropriate control groups used in these studies.

Although the possibility of such limitations cannot be totally excluded, the general paucity of persistent neurological effects on PE and NB testing is striking, especially in light of the magnitude of exposures in some of these cohorts.

Conclusion

Our review of previous-exposure studies finds consistent evidence that Hg⁰-related neurotoxic effects detectable on PE, NB testing, and EPS are substantially reversed over time. To the extent that such effects do persist, they are reported principally in workers who have had very high dose exposures. In addition, based on limited available data, those effects reported to persist have been described as having little or no functional significance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We wish to thank Ms. J. Rivera for bibliographic excellence. We are very grateful to the four anonymous reviewers selected by the Editor for the value of their comments in improving the manuscript.

Dr. Louis was supported by grant R01 NS094607 from NINDS.

References

- Adams CR, Ziegler DK, Lin JT. Mercury intoxication simulating amyotrophic lateral sclerosis. *J Am Med Assoc.* 1983; 250:642–643.
- Albers JW, Cavender GD, Levine SP, Langolf GD. Asymptomatic sensorimotor polyneuropathy in workers exposed to elemental mercury. *Neurology.* 1982; 32:1168–1174. [PubMed: 6289189]
- Albers JW, Kallenbach LR, Fine LJ, Langolf GD, Wolfe RA, Donofrio PD, Alessi AG, Stolp-Smith KA, Bromberg MB. Neurological abnormalities associated with remote occupational elemental mercury exposure. *Ann Neurol.* 1988; 24:651–659. [PubMed: 2849369]
- [ACGIH] American Conference of Governmental Industrial Hygienists. 2012 Threshold Limit Values (TLVs) for Chemical Substances and Physical Agents and Biological Exposure Indices (BEIs). Cincinnati, American Conference of Governmental Industrial Hygienists. 2012
- [ACGIH] American Conference of Governmental Industrial Hygienists. Mercury, Elemental: BEI® 7th Edition Documentation. Cincinnati, American Conference of Governmental Industrial Hygienists. 2013
- Andersen A, Ellingsen DG, Morland T, Kjuus H. A neurological and neurophysiological study of chloralkali workers previously exposed to mercury vapour. *Acta Neurol Scand.* 1993; 88:427–433. [PubMed: 8116345]
- Angotzi G, Battistini N, Carboncini F, Cioni R, Desideri E, Paradiso C, Nuti D, Sartorelli E. Impairment of nervous system in workers exposed to inorganic mercury. *Toxicol Eur Res.* 1981; 3:275–278. [PubMed: 7330870]
- Baker EL, Letz R, Fidler A. A computer-administered neurobehavioral evaluation system for occupational and environmental epidemiology. Rationale, methodology, and pilot study results. *J Occup Med.* 1985; 27:206–212. [PubMed: 3981277]
- Barr DB, Wilder LC, Caudill SP, Gonzalez AJ, Needham LL, Pirkle JL. Urinary creatinine concentrations in the U.S. population: implications for urinary biologic monitoring measurements. *Environ Health Perspect.* 2005; 113:192–200. [PubMed: 15687057]
- Bast-Pettersen R, Ellingsen DG, Efskind J, Jordskogen R, Thomassen Y. A neurobehavioral study of chloralkali workers after the cessation of exposure to mercury vapor. *Neurotoxicology.* 2005; 26:427–437. [PubMed: 15935213]
- Bidstrup PL, Bonnell JA, Harvey DG, Locket S. Chronic mercury poisoning in men repairing direct - current meters. *Lancet.* 1951; 2:856–861. [PubMed: 14881485]
- Bluhm RE, Bobbitt RG, Welch LW, Wood AJJ, Bonfiglio JF, Sarzen C, Heath AJ, Branch RA. Elemental mercury vapour toxicity, treatment, and prognosis after acute, intensive exposure in chloralkali plant workers. Part I: history, neuropsychological findings and chelator effects. *Hum Exp Toxicol.* 1992; 11:201–210. [PubMed: 1352115]
- Buijink AW, Contarino MF, Koelman JH, Speelman JD, van Rootselaar AF. How to tackle tremor - systematic review of the literature and diagnostic work-up. *Front Neurol.* 2012; 3:146. [PubMed: 23109928]
- Camerino D, Cassitto MG, Desideri E, Angotzi G. Behavior of some psychological parameters in a population of a Hg extraction plant. *Clin Toxicol.* 1981; 18:1299–1309. [PubMed: 7341056]
- Chaffin, DB., Dinman, BD., Miller, JM., Smith, RG., Zontine, DH. An Evaluation of the Effects of Chronic Mercury Exposures on EMG and Psychomotor Functions (HSM-099-71-62 Final Report). National Institutes of Health; 1973.
- Cordeiro Q Jr, de Araujo Medrado FM, Fraguas R Jr. Depression, insomnia, and memory loss in a patient with chronic intoxication by inorganic mercury. *J Neuropsychiatry Clin Neurosci.* 2003; 15:457–458. [PubMed: 14627777]
- Ellingsen DG, Bast-Pettersen R, Efskind J, Thomassen Y. Neuropsychological effects of low mercury vapor exposure in chloralkali workers. *Neurotoxicology.* 2001; 22:249–258. [PubMed: 11405256]
- Ellingsen DG, Morland T, Andersen A, Kjuus H. Relation between exposure related indices and neurological and neurophysiological effects in workers previously exposed to mercury vapour. *Br J Ind Med.* 1993; 50:736–744. [PubMed: 8398861]
- Fawer RF, DeRibaupierre Y, Gullemin MP, Berode M, Lob M. Measurement of hand tremor induced by industrial exposure to metallic mercury. *Br J Ind Med.* 1983; 40:204–208. [PubMed: 6830719]

- Florentine MJ, Sanfilippo DJ. Elemental mercury poisoning. *Clin Pharm*. 1991; 10:213–221. [PubMed: 1645633]
- Frumkin H, Letz R, Williams PL, Gerr F, Pierce M, Sanders A, Elon L, Manning CC, Woods JS, Hertzberg VS, Mueller P, Taylor BB. Health effects of long-term mercury exposure among chloralkali plant workers. *Am J Ind Med*. 2001; 39:1–18. [PubMed: 11148011]
- Gonzalez-Usigli, HA., Espay, A. Whitehouse Station: Merck & Company, Inc; 2013. Tremor: A Merck Manual of Patient Symptoms podcast. (http://www.merckmanuals.com/professional/neurologic_disorders/movement_and_cerebellar_disorders/tremor.html)
- Gunther W, Sietman B, Seeber A. Repeated neurobehavioral investigations in workers exposed to mercury in a chloralkali plant. *Neurotoxicology*. 1996; 17:605–614. [PubMed: 9086481]
- Hashiba T. A research on the mercury poisoning of miners (Report 1-5) [in japanese]. *Hokkaidou J Med Sci*. 1954; 29:282–341.
- He FS, Zhou XR, Lin BX, Xiung YP, Chen SY, Zhang SL, Ru JY, Deng MH. Prognosis of mercury poisoning in mercury refinery workers. *Ann Acad Med Singapore*. 1984; 13(2 suppl):389–393. [PubMed: 6497343]
- International Programme on Chemical Safety. Concise International Chemical Assessment Document 50: Elemental Mercury and Inorganic Mercury Compounds: Human Health Aspects. Geneva: World Health Organization; 2003.
- Johnson, BL., Baker, EL. Prevention of Neurotoxic Illness in Working Populations. New York: Wiley; 1987.
- Kallenbach, LR. Health evaluation and reported symptoms in workers with past exposure to elemental mercury (unpublished dissertation). Ann Arbor: University of Michigan; 1988.
- Kishi R, Doi R, Fukuchi Y, Satoh H, Satoh T, Ono A, Moriwaka F, Tashiro K, Takahata N. Subjective symptoms and neurobehavioral performances of ex-mercury miners at an average of 18 years after the cessation of chronic exposure to mercury vapor. *Environ Res*. 1993; 62:289–302. [PubMed: 8344236]
- Kishi R, Doi R, Fukuchi Y, Satoh H, Satoh T, Ono A, Moriwaka F, Tashiro K, Takahata N, Sasatani H, Shirakashi H, Kamada T, Nakagawa K. Residual neurobehavioural effects associated with chronic exposure to mercury vapour. *Occup Environ Med*. 1994; 51:35–41. [PubMed: 8124461]
- Langolf GD, Chaffin DB, Henderson R, Whittle HP. Evaluation of workers exposed to elemental mercury using quantitative tests of tremor and neuromuscular functions. *Am Ind Hyg Assoc J*. 1978; 39:976–984. [PubMed: 742601]
- Langolf GD, Smith PJ, Henderson R, Whittle H. Measurements of neurological functions in the evaluations of exposure to neurotoxic agents. *Ann Occup Hyg*. 1981; 24:293–296. [PubMed: 7316329]
- Langworth S, Almqvist O, Soderman E, Wikstrom BO. Effects of occupational exposure to mercury vapour on the central nervous system. *Br J Ind Med*. 1992; 49:545–555. [PubMed: 1515346]
- Letz R, Gerr F, Cragle D. Residual neurological deficits 30 years after occupational exposure to elemental mercury. *Neurotoxicology*. 2000; 21:459–474. [PubMed: 11022856]
- Levine SP, Cavender GD, Langolf GD, Albers JW. Elemental mercury exposure: Peripheral neurotoxicity. *Br J Ind Med*. 1982; 39:136–139. [PubMed: 6279139]
- Liang YX, Sun RK, Sun Y, Chen ZQ, Li LH. Psychological effects of low exposure to mercury vapor: Application of a computer-administered neurobehavioral evaluation system. *Environ Res*. 1993; 60:320–327. [PubMed: 8472661]
- Louis ED, Yousefzadeh E, Barnes LF, Yu Q, Pullman SL, Wendt KJ. Validation of a portable instrument for assessing tremor severity in epidemiologic field studies. *Movement Disorders*. 2000; 15:95–102. [PubMed: 10634247]
- Louis ED. Kinetic tremor: differences between smokers and non-smokers. *Neurotoxicology*. 2007; 28:569–575. [PubMed: 17267044]
- Mathiesen T, Ellingsen DG, Kjuus H. Neuropsychological effects associated with exposure to mercury vapor among former chloralkali workers. *Scand J Work Environ Health*. 1999; 5:342–350.
- McCullough JE, Dick R, Rutchik J. Chronic mercury exposure examined with a computer-based tremor system. *J Occup Environ Med*. 2001; 43:295–300. [PubMed: 11285879]

- Meyer-Baron M, Schaeper M, Seeber A. A meta-analysis for neurobehavioral results due to occupational mercury exposure. *Arch Toxicol.* 2002; 76:127–136. [PubMed: 11967617]
- Meyer-Baron M, Schaeper M, van Thriel C, Seeber A. Neurobehavioural test results and exposure to inorganic mercury: in search of dose-response relations. *Arch Toxicol.* 2004; 78:207–211. [PubMed: 14598023]
- Miller JM, Chaffin DB, Smith RG. Subclinical psychomotor and neuromuscular changes in workers exposed to inorganic mercury. *Am Ind Hyg Assoc J.* 1975; 36:725–733. [PubMed: 1180206]
- Moriwaka F, Tashiro K, Doi R, Satoh H, Fukuchi Y. A clinical evaluation of the inorganic mercurialism--its pathogenic relation to amyotrophic lateral sclerosis. *Rinsho Shinkeigaku.* 1991; 31:885–887. [PubMed: 1764867]
- National Institute of Neurological Disorders and Stroke (NINDS). Tremor (NIH Publication No 12-4734). Bethesda: National Institute of Neurological Disorders and Stroke, National Institute of Health; 2012.
- National Research Council. Environmental Neurotoxicology. Washington, DC: The National Academies Press; 1992.
- Powell TJ. Chronic neurobehavioural effects of mercury poisoning on a group of Zulu chemical workers. *Brain Injury.* 2000; 14:797–814. [PubMed: 11030454]
- Reh, CM., Deitchman, SD., Moss, CE. NIOSH Health Hazard Evaluation Report: HETA: 87-402-2145, LCP Chemicals and Plastics, Inc, Brunswick Georgia. Cincinnati: National Institute for Occupational Safety and Health, Centers for Disease Control; 1991.
- Roels H, Abdeladim S, Braun M, Malchaire J, Lauwerys R. Detection of hand tremor in workers exposed to mercury vapour: a comparative study of three methods. *Environ Res.* 1989; 49:152–165. [PubMed: 2753003]
- Roels H, Lauwerys R, Buchet JP, Bernard A, Barthels A, Oversteens M, Gaussin J. Comparison of renal function and psychomotor performance in workers exposed to elemental mercury. *Int Arch Occup Environ Health.* 1982; 50:77–93. [PubMed: 7085088]
- Schaumburg HH, Spencer PS. Recognizing neurotoxic disease. *Neurology.* 1987; 37:276–278. [PubMed: 3808308]
- Sternberg EJ, Alcalay RN, Levy OA, Louis ED. Postural and intention tremors: a detailed clinical study of essential tremor vs. Parkinson's disease. *Front Neurol.* 2013; 4(Article 51):1–8. [PubMed: 23355832]
- Suwa N, Takahata N. Clinical studies of chronic inorganic mercury poisoning [in japanese]. *Rec Adv Res Nerv System.* 1969; 13:89–92.
- Triebig G, Schaller KH. Neurotoxic effects in mercury--exposed workers. *Neurobehav Toxicol Teratol.* 1982; 4:717–720. [PubMed: 7170033]
- Urban P, Lukas E, Nerudova J, Cabelkova Z, Cikrt M. Neurological and electrophysiological examinations on three groups of workers with different levels of exposure to mercury vapors. *Eur J Neurol.* 1999; 6:571–577. [PubMed: 10457390]
- Verberk MM, Salle HJA, Kemper CH. Tremor in workers with low exposure to metallic mercury. *Am Ind Hyg Assoc J.* 1986; 47:559–562. [PubMed: 3766401]
- Vroom FQ, Greer M. Mercury vapour intoxication. *Brain.* 1972; 95:305–318. [PubMed: 4144038]
- Wastensson G, Lamoureux D, Sallsten G, Beuter A, Barregard L. Quantitative tremor assessment in workers with current low exposure to mercury vapor. *Neurotoxicol Teratol.* 2006; 28:681–693. [PubMed: 17056227]
- White RF, Feldman RG, Moss MB, Proctor SP. Magnetic resonance imaging (MRI), neurobehavioral testing, and toxic encephalopathy: two cases. *Environ Res.* 1993; 61:117–123. [PubMed: 8472665]
- Williams PL, Frumkin H, Pierce ML, Manning CC, Elon L, Sanders AG. Reconstruction of occupational mercury exposures at a chloralkali plant. *Occup Environ Med.* 2001; 58:81–86. [PubMed: 11160985]
- Wood RW, Weiss AB, Weiss B. Hand tremor induced by industrial exposure to inorganic mercury. *Arch Environ Health.* 1973; 26:249–252. [PubMed: 4696382]
- World Health Organization. Environmental Health Criteria 118: Inorganic Mercury. Geneva: World Health Organization; 1991.

Zedda S, Cirila AM, Ratti R, Sala C, Zampollo A. Rischio da mercurio nella fabbricazione di lampade fluorescenti studio clinico e ambientale. *G Ital Med Lav.* 1980; 2:187–192.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Exp. Cat.	Cohorts	U _{Hg}	PE	Tremor	MC	DTRs	Strength	Balance	Sensory	PN
h	Hokkaido 1993	>500		(-) [‡]	(-) [‡]	(-) [‡]		(-)		
h	Albers 1988	260		(-)	(-)	(-)	(-)		(+)	(-)
h	Letz 2000	201	(-)	(-)	(-)	(-)	(-)		(+)	NR [¶]
m	Ellingsen 1993	108*		(-)	(+)	(-)		(-)	(+)	(-)
l	Frumkin 2001	72 [†]	(-)	NR	NR	NR	NR	NR	NR	(-)

(+)	positive finding		no data
(-)	null finding	NR	testing performed, but results not reported

Figure 1.

Overview of occupational cohort studies that evaluated the association between previous exposure to elemental mercury vapor and PE outcomes. Studies are listed top to bottom by decreasing group mean UHg values (µg/L) in exposed workers, and category of exposure is denoted (h = high, m = medium, l = low). Abbreviations: DTR: deep tendon reflexes; Exp. Cat.: exposure category; MC: motor coordination; NR: not reported; PE: physical examinations; PN = peripheral neuropathy. *UHg value was converted to µg/L from units originally reported in study, as detailed in Table 1. [†]Approximation of group mean, based on urine mercury levels from 78 workers (see text for details). [‡]Moriwaka et al. (1991) did not evaluate statistical significance of findings (see text for details). [¶]Results for PN based on a combination of results from PE and other forms of testing (i.e. NB testing and EPS).

Exp. Cat. Cohorts	U _{Hg} *	NB Tremor subtypes												Color		
		NB Tremor subtypes						Motor function†			Motor accuracy†			Sensory	Vision	Balance
		Postural		Intention		Kinetic		Dext	Speed	Strength	Speed	Reaction time				
		Phy	HE	Phy	HE	Phy	HE				SD	SRT	CPT			
h Hokkaido 1993	>500				(+)	(+) track	(+) track	(+)	(+)	(+)		(+)				(-)
h Albers 1988	260	(-)				(-) BGT	(-) track	(-)		(-)	(-)	(-)		(-)		
h Letz 2000	201	(-)				(-) track	(-) track	(-)	(-)	(-)	(-)	(-)		(-)		(-)
m Ellingsen 1993	108*		(-)			(-) track	(+) BVRT	(+)			(-)	(-)	(-)			
l Frumkin 2001	72†	(+)				(-) track	(-) track	(+)	(+)	(-)	(-)	(-)		(+)	(-)	(-)
b Bast-Petersen 2005	23*	(-)	×			(-) BVRT	(-) BVRT	(-)	(-)		(-)		(-)			

(+) significant finding
 (-) null finding
 × paradoxical finding
 no data

Figure 2.

Overview of occupational cohort studies that evaluated the association between previous exposure to elemental mercury vapor and six neurobehavioral outcomes. Studies are listed top to bottom by decreasing group mean UHg values (µg/L), and category of exposure is denoted (h = high, m = medium, l = low, b = BEI). Abbreviations: BVRT: Benton Visual Retention Test; CPT: Continuous Performance Test; Dext: dexterity; HE: hand-eye coordination tests of motor steadiness used to measure NB tremor; NB: neurobehavioral; Phy: physiological tests of NB tremor; SD: Symbol Digit/Digit Symbol; SRT: Simple Reaction Time. *Indicates UHg was converted to µg/L from units originally reported in study as described in the Methods section. †Results of motor steadiness tests were tabulated as Tremor (see HE columns for Postural, Intention and Kinetic tremor).

Cat.	Cohorts	U _{Hg}	NCS				VEPs	
			NCV	AMP	LAT	LR	AMP	LAT
h	Albers 1988	260	(-)	(-)	(-)	(-)		
h	Letz 2000	201	(+)	(-)	(-)			
m	Ellingsen 1991	108*	(-)	(-)	(-)	(-)	(-)	(-)
l	Frumkin 2001	72 [†]	(+)	(-)		(-)		

(+)	positive finding		no data
(-)	null finding		

Figure 3.

Overview of occupational cohort studies that evaluated the association between previous exposure to elemental mercury vapor and two types of electrophysiological outcomes (NCS, and VEPs). Studies are listed top to bottom by decreasing group mean UHg values (µg/L), and category of exposure is denoted (h = high, m = medium, l = low). Abbreviations: AMP: amplitude; LAT: latency; LR: late responses (F-wave latencies); NCS: nerve conduction studies; NCV: nerve conduction velocity; VEPs: visual evoked potentials. *UHg value was converted to µg/L from units originally reported in study, as detailed in Table 1.

[†]Approximation of group mean, based on UHg levels from 78 workers.

Figure 4.
Improvement of tremor following cessation of exposure.

Table 1
Descriptive characteristics of previous-exposure cohorts included in the systematic review

Cohort	Population	Age mean $\pm$ SD (range)	Historical exposures ($\mu\text{g/L}$, unless otherwise specified) metric mean $\pm$ SD (range)	Years of exposure mean (range)	Years since exposure mean (range)
Bast-Pettersen Norway 2005	49 chloralkali workers 49 unexposed workers	46 (29-67) 46 (28-69)	Ave 23* Cum 310* Peak NR (7-63) (36-1216) (NR)	13.1 (2.8-34.5)	4.8 (4.2-10.0)
Franklin USA 2001	147 chloralkali workers 132 community workers	50 $\pm$ 13 49 $\pm$ 12	Mean 72 [†] Cum <300 $\mu\text{g}/\text{m}^3$ Peak <90 $\mu\text{g}/\text{m}^3$ (13-173) (2-903) (7-147)	7.0 (1-38)	5.7 (0-35)
Ellingsen Norway 1993	77 chloralkali workers 53 nitrate fertilizers	45 (NR) 46 (NR)	Mean 108* Cum 649* Peak 108* (8-584) (33-3446) (NR)	7.9 (1.1-36.2)	12.3 (1-35)
Letz USA 2000	104 lithium workers 101 unexposed workers	70 $\pm$ 6 71 $\pm$ 7	Mean 201 $\pm$ 98 Cum 3362 $\pm$ 1177 Peak 635 $\pm$ 320 (64-6956) (1089-6588) (187-1900)	4.8 (0.75-12.7)	30+ (NR)
Albers USA 1988	247 lithium workers 255 unexposed workers	64 $\pm$ 7 64 $\pm$ 7	Mean 260 [‡] Cum 3595 $\pm$ 1191 Peak 647 $\pm$ 369 (NR) (2144-8572) (166-3022)	5.3 (0.33-NR)	21 (20-35)
Hokkaido Japan 1993	76 Hg miners 76 community residents	60 $\pm$ 7 age matched	Mean >500 Cum NR Peak NR [§] 22.8% >2000 72.4% 500-2000 4.8% <500 (300-3500) [¶] (NR) (NR)	15.5 (1-42)	17.9 (2-29)

Key:

* Urine Hg values were converted from originally reported units (nmol/mmolcreatinine) to micrograms per liter ($\mu\text{g/L}$) by first converting to units of $\mu\text{g/g}$ creatinine and then multiplying by 1.4 g/L ; the mid-point of the upper and lower bound of the expected range of urine creatinine concentration in the US population (Barr et al. 2005).

[†] Approximation of group mean, based on urine mercury levels from 78 workers (see text for details).

[‡] weighted average of mean Urine Hg 1955-1956 (Table 4, Albers 1988).

[¶] Urine Hg range during 1950-1951, as reported in Hashiba 1954; range reported in Suwa 1969 was 50-2560 $\mu\text{g/L}$.

[§] Mean Peak level not reported; distribution of peak levels is provided below.
Abbreviations: Ave = average; Cum = cumulative; NR = not reported.

Table 2
Summary of PE outcomes in current- and previous-exposure studies, overall and by exposure categories

PE outcomes	Proportion of studies with abnormal findings on PE*			
	Overall (L, M, H)	Low	Medium	High
Tremor:	Current studies [†]	30% (3/10)	10% (1/10)	78% (14/18)
	Previous studies	0% (0/1)	0% (0/1)	0% (0/3)
Motor Coordination:	Current studies [†]	50% (1/2)	33% (1/3)	89% (7/8)
	Previous studies	0% (0/1)	100% (1/0)	0% (0/3)
Deep Tendon Reflexes:	Current studies [†]	0% (0/2)	0% (0/4)	90% (9/10)
	Previous studies	0% (0/1)	0% (0/1)	0% (0/3)
Sensory Function:	Current studies [†]	0% (0/1)	0% (0/1)	80% (4/5)
	Previous studies	0% (0/1)	100% (1/0)	67% (2/3)

KEY:

* The percentage and number of cohort studies that reported abnormal findings divided by the number of studies that specifically indicated evaluating that outcome. A number of current-exposure studies did not specifically indicate testing of MC, DTRs or sensory function; these were not included in this table. All previous-exposure studies evaluated each of these outcomes. Because PE was not performed in the BEI previous-exposure cohort, the comparison of PE outcomes between previous- and current-exposure studies is limited to results from studies belonging to the Low, Medium, and High Exposure categories.

[†] Does not include data from 2 High exposure studies with unique designs: Vroom and Greer 1972 selected workers based on the severity of their effects, and Albers et al. 1982 evaluated workers using a nested case-control design.

Table 3
Summary results of NB outcomes in studies of currently- and previously-exposed workers: assessment of dose-relatedness

NB outcomes	Proportion of studies with significant results [*]						Group Mean U _{Hg} (µg/L) [†]		Dose-response [‡]	
	Overall	<BEI	Low	Med	High	All groups	Significant vs. null results	Individual study results		
All NB Tremor:	Current	62% (13/21)	38% (3/8)	50% (2/4)	75% (3/4)	100% (5/5)	116 µg/L	169 vs. 41	60% (6 of 10)	
	Remote	67% (4/6)	0% (0/1)	100% (1/1)	100% (1/1)	67% (2/3)	188 µg/L	203 vs. 122	100% (5 of 5)	
POSTURAL Tremor:	Current	65% (11/17)	33% (2/6)	67% (2/3)	67% (2/3)	100% (5/5)	130 µg/L	184 vs. 39	50% (6 of 12)	
	Previous	20% (1/5)	0% (0/1)	100% (1/1)	0% (0/1)	0% (0/2)	141 µg/L	72 vs. 160	50% (2 of 4)	
KINETIC Tremor:	Current	14% (1/7)	0% (0/4)	0% (0/1)	0% (0/1)	100% (1/1)	70 µg/L	276 vs. 42	75% (3 of 4)	
	Previous	50% (3/6)	0% (0/1)	0% (0/1)	100% (1/1)	67% (2/3)	190 µg/L	246 vs. 106	80% (4 of 5)	
INTENTION Tremor:	Current	57% (4/7)	50% (1/2)	50% (1/2)	67% (2/3)	NT	80 µg/L	81 vs. 77	0% (0 of 5)	
	Previous	100% (1/1)	NT	NT	NT	100% (1/1)	500 µg/L	>500 vs. NA	100% (1 of 1)	
Manual dexterity:	Current	56% (5/9)	25% (1/4)	100% (1/1)	100% (1/1)	67% (2/3)	166 µg/L	204 vs. 53	75% ^c (3 of 4)	
	Previous	50% (3/6)	0% (0/1)	100% (1/1)	100% (1/1)	33% (1/3)	212 µg/L	209 vs. 215	100% (3 of 3)	
Motor speed:	Current	56% (5/9)	33% (2/6)	NT	100% (1/1)	100% (2/2)	108 µg/L	171 vs. 23	67% ^c (2 of 3)	
	Previous	50% (2/4)	0% (0/1)	100% (1/1)	NT	50% (1/2)	202 µg/L	252 vs. 133	50% (1 of 2)	

Table presents summary results for NB tests of tremor (all types combined, and by subtypes) and tests of manual dexterity and motor speed based on comparisons between exposed workers and controls, and summary results from dose-response analyses performed in individual studies.

^{*} The percentage and number of studies with statistically significant outcomes divided by the total number studies that evaluated that outcome, presented for all studies combined (Overall) and by category of exposure.

[†] Weighted average of group mean U_{Hg} levels in the cohorts tested for tremor, and in cohorts with significant vs. null tremor results. NT=not tested.

[‡] Because dose-response was not evaluated in the <BEI study of previously-exposed workers, the comparison of dose-response between previous- and current-exposure studies is limited to results reported in studies belonging to the Low, Medium, and High exposure categories.

Abbreviations: NA = not applicable; NT = not tested

Table 4
Comparison of NCS results and patterns of effect in studies of currently- and previously-exposed workers

NCS outcomes	All NCS*	Sensory vs.	Motor	Upper vs.	Lower Limbs
All NCS outcomes*:					
Current studies:	24% (17/72) [†]	37% (10/27)	16% (7/45)	27% (11/45)	19% (5/27)
Previous studies:	2% (1/49)	0% (0/19)	3% (1/30)	4% (1/28)	0% (0/21)
Velocity:					
Current studies:	17% (6/36)	25% (4/16)	10% (2/20)	13% (3/24)	25% (3/12)
Previous studies:	7% (1/15)	0% (0/7)	13% (1/8)	11% (1/9)	0% (0/6)
Latency:					
Current studies:	41% (7/17)	67% (4/6)	27% (3/11)	55% (6/11)	17% (1/6)
Previous studies:	0% (0/11)	0% (0/5)	0% (0/6)	0% (0/6)	0% (0/5)
Amplitude:					
Current studies:	29% (4/14)	40% (2/5)	22% (2/9)	33% (3/9)	20% (1/5)
Previous studies:	0% (0/15)	0% (0/8)	0% (0/7)	0% (0/9)	0% (0/6)

Table presents the percentage and number of statistically significant NCS outcomes divided by the total number of outcomes evaluated. Results that were not reported, or were paradoxical, were categorized as “null” findings and included in the denominator.

*The comparison of patterns of effect (Sensory vs. Motor, Upper vs. Lower) for ‘All NCS outcomes’ includes NCV, latency, amplitude, and late responses (i.e. F-wave and H-reflexes). The limited number of late responses precluded a separate analysis of their patterns of effect.

[†] Abnormal results were reported for a total of 21 of the 72 outcomes tested on NCS; four outcomes that were described by study authors as “abnormal” were not tabulated in the numerator because neither study reported the statistical significance of their findings (Urban 1999; Zampollo 1987).