Epidemiological Study Critical Evaluation Form

Reference:	Frumkin, H., Letz, R., Williams, P.L., Gerr, F., Pierce, M., Sanders, A., Elon, L., Manning, C.C., Woods, J.S., Hertzberg, V.S., Mueller, P. and B. Brooks Taylor. 2001. Health effects of long-term mercury exposure among chloralkali plant workers. Am J Indust Med 39: 1-18.
Toxicological Endpoint:	Neurological and Renal

Criteria	
Peer reviewed:	
Type of study:	Retrospective cohort study
Population(s) studied:	Occupational: chloralkali plant
Case identification/definition	
Sample size:	147
Stratification (age, sex, etc.):	Age, sex and race.
Control identification/definition	
Sample size:	132
Matching Criteria:	Controls selected by random sampling from three local employers, and were matched to exposed workers based upon age, sex and race.
Group selection method:	Employees of a the chloralkali plant in Brunswick, GA, employed for at least 1 year between 1956 and 1994 (when closed). Comparison group recruited from three employers located in and near Brunswick.
Data source for group information:	Interviews, and personnel and industrial hygiene sampling records.
Outcome(s) studied:	Nerve conduction, sensory/motor, standing steadiness, and tremor tests, computer-based neuropsychological tests and traditional neuropsychological tests.
Exposure definition:	Workers exposed for a duration of more than one year in a chloralkali plant. The mean time since the last exposure at the plant was about 5.7 years.
Exposure measurement:	HgU data for the interval 1988-1991 was assessed and compared to calculated cumulative exposures. Two HgU samples were collected from each participant during the study. Blood samples were collected for assessment of HgB levels.
Duration of exposure applicable to measurement (i.e. acute, chronic):	Chronic

Exposure levels:	Average exposure levels in the clean areas of the plant were found to range from 10-20 $\mu g/m^3$, and from 40-50 $\mu g/m^3$ in areas of higher exposure. The maximum exposure level ranged from 7-147 $\mu g/m^3$, however the majority of subjects were found to be exposed to less than 90 $\mu g/m^3$. Cumulative exposures were found to be, in general, lower than 300 $\mu g/m^3$-years.
Data adjustments:	Data was transformed when necessary (by log, square-root, inverse, van der Werden) to normalize the distributions. If the transformations were not successful, the variable was dichotomized at a logical value. Bonferroni's adjustment for multiple testing was applied when necessary to exposure variables. The variables of age, sex, height, body mass index, limb temperature, other mercury exposures, other neurotoxin exposure, amalgam fillings, alcohol consumption, education and medication use were taken into consideration during modeling.
Results	
Relative Risk, Odd Ratio, Confidence Interval:	The survey-reported incidence of miscarriages (17.1% in exposed workers and 9.2% of unexposed workers) approached statistical significant. OR= 2.03, P=0.063).
Statistics	
Procedures/tests:	Spearmans' correlation coefficient; Chi square test; Fisher's exact test; polytomous logistic regression; linear regression analysis
Statistically significant findings:	Exposed subjects reported a higher prevalence of symptoms, and symptoms of greater severity, than the control group. Significant differences between the exposed and control group were observed: increased peroneal nerve conduction velocity, increased tremor, increased vibrotactile thresholds in fingers and toes, fewer finger taps, slower performance in the pegboard task, and poorer performance in the Hopkins Verbal Learning Test. When exposure was modeled as a continuous variable as an average/cumulative exposure, high cumulative exposure was associated with decreased proximal ulnar motor nerve velocity and distal ulnar nerve sensory velocity. Higher mean exposure was associated with poorer performance in the grooved pegboard test and higher maximum exposure was associated with decreased distal ulnar sensory nerve velocity and poorer vocabulary score.
Non-statistically significant findings:	No significant differences in current HgU levels were observed between exposed and control subjects. No significant differences in renal effects or clearance were observed.
Dose response presence/absence:	Not available

Biases identified by the authors:	Although determined to be unlikely, confounding factors may have masked true associations between exposure and effect. Errors in exposure assessment may have introduced bias (ie. the exclusion of dermal exposure/absorption in the assessment). Selection bias may have affected the results, as less than half of the workers could be contacted. Demographic data were not available to compare characteristics of the exposed and unexposed groups.
Assumptions/limitations of the study:	The exposure levels in the plant may have been too low to demonstrate toxicity. Due to the number of workers exposed to higher levels of Hg, the study may have lacked sufficient statistical power. The 5.7 years since the last exposure may have resulted in the absence of strongly positive findings. Exposed subjects may have experienced effects in the past, which were reversed over time.
Conclusions:	Workers exposed to Hg reported more symptoms than unexposed control workers, however no strong associations between neurological or renal function and Hg exposure were observed. Authors note that it is possible that short term mercury neurotoxicity may be resolved within a few years after cessation of the exposure, but that subtle chronic effects may appear over time along with normal age-related changes.
Reviewer Comments	Two 24-hour urine samples were collected from each subject during study, but it is not evident if historical samples were spot-test or 24-hour samples. Current urine samples corrected for creatinine; not evident if historical samples were corrected for creatinine.

Information for Dose Response Assessment	A significant association between Hg exposure and neurological effects was found. However, since almost 6-years had passed since the time of the last Hg exposure, the accuracy of correlating HgU levels with exposure is questionable. Information concerning mercury concentrations in air during the exposure period were characterized through historical records. However, few significant associations between mercury exposure and symptoms were identified. The authors identified that the number of significant findings was similiar to the expected by chance. This study is not recommended for inclusion in the dose-response assessment.

Epidemiological Study Critical Evaluation Form

Reference:	Haut, M.W., Morrow, L.A., Pool, D., Callahan, T.S., Haut, J.S., and M.D. Franzen. 1999. Neurobehavioral effects of acute exposure to inorganic mercury vapor. Appl. Neuropsychol. 4: 193-200.
Toxicological Endpoint:	Neurological

Criteria	
Peer reviewed:	Unknown
Type of study:	
Population(s) studied:	Occupational: Sheet metal workers
Case identification/definition	
Sample size:	13
Stratification (age, sex, etc.):	None
Control identification/definition	
Sample size:	13
Matching Criteria:	Age and education.
Group selection method:	Exposed participants were employees that had a 2 to 4 week period of Hg exposure during sheet metal work. Average HgB level was reported to be 48.7 µg/L, and ranged from 21-84 µg/L. The patients were referred by their physician or attorney.
Data source for group information:	Unclear how exposure group information obtained. Author indicates that the patients reported their information. Controls completed a screening questionnaire.
Outcome(s) studied:	Neuropsychological effects, measured by Cognitive Tests (motor skills, visuoperception, language, attention, speeded processing, verbal learning and memory, nonverbal learning and memory and abstraction and problem solving) and Minnesota Multiphasic Personality Inventory (MMPI) test.
Exposure definition:	Exposed over a 2 to 4 week period.
Exposure measurement:	Mercury concentrations in blood (HgB), air samples, in the paint (on the sheet metal) and in the flyash were determined after exposure was terminated.
Duration of exposure applicable to measurement (i.e. acute, chronic):	acute/short-term
Exposure levels:	Average HgB of 48.7 µg/L (range of 21 to 84 µg/L). Air concentrations up to 80 µg/m^3. Concentrations of 1.7 and 0.87 µg/g in paint and flyash, respectively.
Data adjustments:	Neuropsychological tests were grouped into cognitive clusters (confirmed by correlation) to control for multiple comparisons.
Results	

Relative Risk, Odd Ratio, Confidence Interval:	Not applicable
Statistics	
Procedures/tests:	Multivariate analysis: examine performance between exposed and nonexposed groups on each of the cognitive test clusters.
Statistically significant findings:	Exposed subjects had significantly reduced performance in all cognitive tests relative to controls, with the exception of the attention and nonverbal learning/memory tests. Exposed subjects also had significantly reduced performance in visusoperception, language score, abstraction and problem solving. In the MMPI scales, exposed subjects demonstrated significantly higher scores than controls.
Non-statistically significant findings:	Majority of correlations between emotional state and cognitive function were not significant. Correlations between cognitive test scores and HgB levels were found to be not significant. However, non-significant reductions in performance were observed.
Dose response presence/absence:	Not described
Biases identified by the authors:	The neuropsychological effects observed in this study may be the result of previous, chronic exposure rather than the 2-4 week exposures examined in this study. Previous exposure to other neurotoxins may also have influenced the results by lowering the effect threshold. All patients were also involved in litigation pertaining to the exposure at the time of the study, although there was no evidence of altered results. Many patients reported attempts to minimize their reported deficits to families and significant others to prevent embarrassment.
Assumptions/limitations of the study:	Different levels of exposure over different time periods may result in varying levels of residual neurobehavioural effects.
Conclusions:	Significant impairment in cognitive function and emotional depression were observed in association with Hg exposure. However, no relationship between cognitive function and emotional depression was observed. The observed neuropsychological deficits suggest that frontal and subcortical brain may be involved.
Reviewer Comments	No urine samples were collected during this study. Exposure history was poorly controlled in the study.

Information for Dose-Response Assessment	This study involved the use of HgB monitoring after exposure was terminated (0-20 days). Exposure occurred for a 2-4 week period of time. The half-lives of Hg in red blood cells and plasma, respectively, have been found to be 74- and 80-hours (ACGIH, 2001). Therefore after 3-4 days of exposure, HgB levels would have decreased, potentially influencing the test results. Neurobehavioural effects were not monitored until 10-15 months after the exposure was terminated. Associating HgB levels from the time of exposure with neurobehavioural effects observed almost one year later may not provide complete assessment of the severity of adverse effects. This study therefore is not of use to the dose-response assessment. However, the study does demonstrate that even after a relatively brief exposure, neurobehavioural effects may persist for a much longer period.

Epidemiological Study Critical Evaluation Form

Reference:	Kobal, A.B., Flisar, Z., Miklavcic, V., Dizdarevic, T., and A., Sesek-Briski. 2000. Renal function in miners intermittently exposed to elemental mercury vapour. Arh. Hig. Rada. Toksikol. 51: 369-380.
Toxicological Endpoint:	Renal

Criteria	
Peer reviewed:	Unknown
Type of study:	
Population(s) studied:	Occupational: mercury miners in Slovenia
Case identification/definition	
Sample size:	45
Stratification (age, sex, etc.):	None
Control identification/definition	
Sample size:	Not applicable
Matching Criteria:	Workers served as their own controls, being exposed to contaminated and non-contaminated sites during the study
Group selection method:	Miners who did not meet the exclusion criteria and that had normal electrolphoretic patterns.
Data source for group information:	Questionnaires, medical files, medical examinations and biological monitoring.
Outcome(s) studied:	Renal effects
Exposure definition:	Occupational mercury exposure in mercury mine
Exposure measurement:	Present and historical mercury concentrations in urine (HgU) and mercury levels in indoor air.
Duration of exposure applicable to measurement (i.e. acute, chronic):	Subchronic
Exposure levels:	Average duration of exposure was 37-days (range 6-82)
Data adjustments:	
Results	
Relative Risk, Odd Ratio, Confidence Interval:	Not applicable
Statistics	
Procedures/tests:	Chi-squared test, t-test or paired samples, Pearson's correlation coefficient, analysis of variance.

Statistically significant findings:	Significant increases observed in post-exposure HgU levels in all subgroups of workers. Significant positive correlation between cumulative urinary mercury index and urinary mercury concentrations before exposure. The prevalence of urinary protein composition changes was significantly higher in those miners with increased mercury absorption than the group overall. Workers with low-molecular weight (LMW) urinary protein profiles demonstrated significantly higher urinary N- acetyl-β-D-glucosaminidase (NAG) levels and urinary α1-microglobulin concentrations relative to workers with normal or high-molecular weight (HMW) profiles. Significant, positive correlations between post-exposure HgU and urinary NAG activity.
Non-statistically significant findings:	No correlation found between cumulative urinary mercury index and HgU after exposure, or between HgU before and after exposure. No correlation found between days of exposure and mean TWAs with HgU after exposure. Exposed workers did not display signs or symptoms of micromercurialism or clinical renal impairment. Results of routine blood and urine analyses were within normal limits. However, a statistically significant increase in prevalence of change in urinary protein composition was observed in exposed workers.
Dose response presence/absence:	Not relevant
Biases identified by the authors:	Differences in protein excretion may be the result of individual intra-and intervariability.
Assumptions/limitations of the study:	The intermittent and varying intensity of Hg exposure, and the methods used to assess urinary protein may have significantly affected the study results.
Conclusions:	Changes in urinary protein composition were identified which may be early biomarkers of renal damage, and may have potential use in the assessment of renal function in exposed workers. The changes in urinary albumin, microglobulin and NAG activity were determined to be clinically insignificant.
Reviewer Comments	Shifts in the patterns of urinary proteins may indicate early renal damage (in proximal tubules). Exposed workers were wearing air-purifying helmets with Hg-absorbing filters during the study. The potential effect on the actual amount of Hg should be considered. Spot-urine samples collected before and after exposure period, in the morning.

Information for Dose-Response Assessment	The significant changes in urinary protein composition were not dose-dependent, but were associated with Hg exposure. No other significant renal effects were observed. Average duration of exposure was 37-days (range 6-62). Mean HgU levels after exposure was 69.9 ug/g creatinine. Mean HgU before exposure was 18.5 ug/g creatinine. This study has been included in the dose-response assessment. Although concentrations of Hg was measured in air, the HgU concentration will be used as an indicator of exposure as workers were wearing air-purifying helmets.

Epidemiological Study Critical Evaluation Form

Reference:	Mathiesen, T., Ellingsen, D.G., and H. Kjuus. 1999. Neuropsychological effects associated with exposure to mercury vapor among former chloralkali workers. Scand. J. Work Environ. Health. 25(4): 342-350.
Toxicological Endpoint:	Neurological

Criteria	
Peer reviewed:	Yes
Type of study:	Cross-sectional
Population(s) studied:	Occupational: former chloralkali workers
Case identification/definition	
Sample size:	75
Stratification (age, sex, etc.):	None
Control identification/definition	
Sample size:	52
Matching Criteria:	Age
Group selection method:	Men, below 65 years of age, that had been exposed for more than 1 year between 1947 and 1987 (when the chloralkali plant was open), and had HgU levels monitored during at least four 3-month periods during employment. Control group included men employed by the same company at the same industrial complex who had no known current or past occupational exposure to mercury. Exclusion criteria included alcohol abuse, major head injuries, metabolic disorders, major psychiatric, neurological or other diseases causing severe disability and exposure to other known occupational neurotoxicants above specified levels.
Data source for group information:	Clinical interview regarding job history, life-style habits and medical history. Clinical examination.

Outcome(s) studied:	General intellectual function: WAIS-R vocabulary, similarities and picture completion tests. Memory and Learning: WAIS-R digit span test, word pairs test, serial digit learning test (SDL-8), Benton visual retention test and Kimura recurring figures test. Perceptual-motor speed and reaction time: trailmaking, WAIS-R digit symbol, NES 2 simple reaction-time and NES 2 continuous performance tests. Manual dexterity and visuomotor coordination: NES 2 hand-eye coordination test and Klove/Metthews grooved pegboard and static steadiness test. Visuospatial ability: WAIS-R block design test.
Exposure definition:	Average exposure time was 7.9 (range of 1.1-36.2) years. Time since exposure cessation averaged 12.7 years.
Exposure measurement:	Historical mercury concentrations in urine (HgU), current HgU and mercury concentrations in blood (HgB).
Duration of exposure applicable to measurement (i.e. acute, chronic):	Chronic.
Exposure levels:	Annual mean urinary mercury concentration of 539 (range of 41-2921) nmol/(L·year). The mean duration exposure was found to be 7.9 years (range 1.1-36.2), and the time since exposure cessation averaged 12.7years (range 1-35)
Data adjustments:	Results of WAIS-R tests were age-scaled. Distribution of static steadiness tests parameters were skewed and consequently were log-transformed. Data was stratified according to the exposure duration, intensity of exposure (high and low) and cumulative exposure. The potential confounders of age, shift-work, alcohol consumption, head injuries and vocabulary) were considered during data analysis.
Results	
Relative Risk, Odd Ratio, Confidence Interval:	Not relevant.
Statistics	
Procedures/tests:	ANOVA, factorial ANOVA, multiple linear regression, least square differences
Statistically significant findings:	Significantly reduced performance in the visual retention test and dexterity in exposed subjects relative to controls. Significant differences in visual retention, dexterity and retention error were observed in the 25 subjects determined to have high cumulative exposures (compared to controls).

Non-statistically significant findings:	No significant differences in neuropsychological parameters were observed between controls and the group of exposed subjects with low cumulative exposure.
Dose response presence/absence:	
Biases identified by the authors:	
Assumptions/limitations of the study:	Due to the relatively large exposure-free intervals, some neurological effects may have reversed in some subjects.
Conclusions:	Hg exposure does not significantly affect general intellectual level or logical reasoning ability. However, Hg exposure may be associated with slight, persistent effects on the central nervous system and visual system. Previous exposure to Hg did not appear to have influenced general intellectual ability or reasoning ability.
Reviewer Comments	Cumulative Hg exposure indices calculated for previous workers/exposures based upon historical HgU data and data adjustments. Some variation in the ability of exposure variables to predict effects (intensity of exposure vs. duration of exposure). Authors suggest that this variability may be due to the potential for Hg to cause neurological effects by different mechanisms.

Information for Dose Response Assessment	Hg exposure in this study ceased between 1-35 years before the workers were assessed (mean time since cessation was 12.7 years). The half-life of HgU is about 40-days (ACGIH, 2001). Although an association between exposure and neurological effects was observed, the effects may have reversed and/or lessened in severity or frequency over time. This study should not be included in the dose-response assessment.

Epidemiological Study Critical Evaluation Form

Reference:	Moszczynski, P., Slowinski, S., Rutkowski, J., Bem, S., and D. Jakus-Stoga. 1995. Lymphocites, T and NK cells, in men occupationally exposed to mercury vapours. Int. J. Occup. Med. Environ. Health. 8(1): 49-56.
Toxicological Endpoint:	Immunological

Criteria	
Peer reviewed:	Yes
Type of study:	
Population(s) studied:	Occupational: chlorine factory employees
Case identification/definition	
Sample size:	81 (26 with exposure < 10 years and 55 with exposures from 10 to 31 years)
Stratification (age, sex, etc.):	Gender
Control identification/definition	
Sample size:	36
Matching Criteria:	None
Group selection method:	Exposure group included occupationally exposed males that were not alcoholics, drug addicts or recovering from infectious diseases. The control group included healthy males with no history of exposure to industrial chemicals or harmful physical factors.
Data source for group information:	Medical examination
Outcome(s) studied:	Immunological effects
Exposure definition:	
Exposure measurement:	Mercury concentrations in urine (HgU) and blood (HgB). Mercury concentraitons in historical and present air samples.
Duration of exposure applicable to measurement (i.e. acute, chronic):	Chronic
Exposure levels:	Air concentrations (TWA) of Hg in plant since 1968 varied between 0.024-0.09 mg/m^3 (median 0.036 mg/m^3) . Peak concentrations (TWA) varied between 0.05 - 0.32 mg/m^3. HgU levels were detected within the range 0-240 μg/L and HgB in the range of 0 - 30 μg/L.
Data adjustments:	Not described
Results	
Relative Risk, Odd Ratio, Confidence Interval:	Not relevant.

Statistics	
Procedures/tests:	Shapiro-Wilk Caussian decomposition test to anlayse for normal distribution. Cochran-Cox or Student-t test. Analysis of variance and partial correlation coefficients.
Statistically significant findings:	Significantly increased counts of T-cells (CD3+), T-helper (CD4+) and T-suppressor) (CD8+) were observed in exposed workers. Lesser increases were observed in workers exposed for less than 10-years relative to workers exposed for greater than 10-years. A positive correlation was found between helper-T cell (CD4+) and exposure duration.
Non-statistically significant findings:	No siginficant differences in the absolute count of CD16+ cells were observed between exposed and control subjects, however, a fall in the percentage on Natural Killer cells (NK, or CD16+) was observed in exposed workers.
Dose response presence/absence:	Not evalauated, but correlation between exposure and effect observed
Biases identified by the authors:	Amalgam fillings
Assumptions/limitations of the study:	Ratio of T-helper to T-suppressor cells not evaluated.
Conclusions:	Occupational Hg exposure was associated with T-cell stimulation. The longer the exposure, the higher the degree of stimulation.
Reviewer Comments	Urine spot tests (morning) used in study. CD4+ cell count may be an indicator of Hg exposure. HgB and HgU concentration information, provided as a range of values, is not very useful in the assessment of exposure.

Information for Dose-Response Assessment	TWA for Hg in air ranged from 0.024-0.09 mg/m^3 (median 0.036 mg/m^3). The mean weighted Hg air level was 0.0028 mg/m^3. All exposures were > 1-year. Hg exposures of < and > 10-years were associated with CD4+ proliferation. This study should be included in the assessment. Air concentrations will be used to describe exposure in the dose response assessment. As it is not clear that the changes observed are clinically significant, the effect will be considered a LOEL.

Epidemiological Study Critical Evaluation Form

Reference:	Netterstrom, B., Guldager, B., and J. Heeboll. 1996. Acute mercury intoxication examined with coordination ability and tremor. Neurotoxicology and Teratology. 18(4): 505-509.
Toxicological Endpoint:	Neurological

Criteria	
Peer reviewed:	Yes
Type of study:	
Population(s) studied:	Occupational: accidental exposure in a factory
Case identification/definition	
Sample size:	14 (7 in a high exposure group and 7 in a low exposure group)
Stratification (age, sex, etc.):	None
Control identification/definition	
Sample size:	15 (selected from the same plant)
Matching Criteria:	Age, sex and occupation.
Group selection method:	Potentially exposed workers (from a mercury spill in a factory) that showed HgU of more than 25 nmol/l. Control group was selected from workers from the same factory.
Data source for group information:	Medical examination, surveys
Outcome(s) studied:	Coordination ability, with CATSYS test system, Tremor Index and Tremor Intensity.
Exposure definition:	Acute exposure as a result of a mercury spill. Initial study conducted 18 and 19 days after exposure. Follow-up study conducted approximately 3 months later.
Exposure measurement:	Mercury concentrations in urine (HgU), blood (HgB) and air.
Duration of exposure applicable to measurement (i.e. acute, chronic):	Acute
Exposure levels:	Air measurements a week after the accident showed mercury concentration of 0.15 mg/m3. In high exposure group, HgU was 106.5 (range of 49.5-249) nmol/l . In low group, HgU was 35.2 (range of 25 to 49.5) nmol/l.
Data adjustments:	Not identified
Results	
Relative Risk, Odd Ratio, Confidence Interval:	Not relevant.
Statistics	
Procedures/tests:	Students t-test and paired t-test

Statistically significant findings:	Mean HgU levels in high-exposure group decreased to 48.2 nmol/L and to 7.8 nmol/L, 3- and 16- months after the spill. After 3-months, the workers in the low-exposure group had HgU levels less than 20 nmol/L. Coordination performance was significantly reduced between the high-exposure group and controls after 3 months.
Non-statistically significant findings:	No significant difference in coordination performance was observed between the low-exposure group and controls. Non-statistically significant reductions in Tremor Index scores were observed between the high- and low-exposure groups with each other and relative to controls. Non-significant increases in Tremor Intensity were observed between the high-exposure group with the low-exposure and control groups.
Dose response presence/absence:	
Biases identified by the authors:	Small number of subjects in high-exposure group, random variation, unreported previous Hg exposure all are factors that may have influenced results. High standard deviations observed in exposure groups suggest marked differences in responses.
Assumptions/limitations of the study:	Not identified
Conclusions:	Subclinical neurological effects may result from subacute Hg exposure
Reviewer Comments	Decreases in tremor intensity may indicate gradual recovery over time. HgB levels assessed shortly after time of exposure, however, were not provided by authors. Only HgU data are provided.

Information for Dose-Response Assessment	This study involved two defined Hg exposure groups. However, the exposure was of short duration given that it was associated with a mercury spill in the workplace. Upon clean-up, the exposure would have ceased. This study used HgU as a indicator of exposure. However, HgU monitoring is more appropriate for chronic exposures. In addition, the HgU levels were not adjusted for creatinine. This study should not be included in the dose-response assessment.

Epidemiological Study Critical Evaluation Form

Reference:	Park, S.H., Araki, S., Nakata, A., Kim, Y.H., Park, J.A., Tanigawa, R., Yokoyama, K., and H. Sato. 2000. Effects of occupational metallic mercury vapour on suppressor-inducer (CD4+CD45RA+) T lymphocytes and CD57+CD16+ natural killer cells. Int Arch Occup Environ Health 73(8): 537-542.
Toxicological Endpoint:	Immunological

Criteria	
Peer reviewed:	Yes
Type of study:	
Population(s) studied:	Occupational: fluorescent-lamp makers
Case identification/definition	
Sample size:	20
Stratification (age, sex, etc.):	all male
Control identification/definition	
Sample size:	20 (selected from the same factory)
Matching Criteria:	Gender, age and smoking.
Group selection method:	
Data source for group information:	Medical examinations
Outcome(s) studied:	Effects on T-lymphocytes: total CD3+, total CD4+, total CD8+, CD4+CD45RA+, CD4+CD45RO+; Natural Killer Cells: CD57+CD16-, CD57+CD16+ and CD57-CD16+. Effects on B-lymphocytes: total CD19+; Total Lymphocytes; Serum Immunoglobulins: IgG, IgA, and IgM).
Exposure definition:	Mean exposure to mercury was 31 (range of 4 to 62) months.
Exposure measurement:	Mercury concentrations in urine (HgU) of exposed group.
Duration of exposure applicable to measurement (i.e. acute, chronic):	
Exposure levels:	Shift time-weighted average (TWA) value for air mercury concentrations at work was 0.0041 mg/m^3. Average HgU was 44.8 (range of 1.8 to 163.5) µg/L.
Data adjustments:	
Results	
Relative Risk, Odd Ratio, Confidence Interval:	Not relevant.
Statistics	
Procedures/tests:	Paired-sample t-test; Stepwise multiple regression analysis

Statistically significant findings:	Significant decreases in total CD4+ and CD4+45RA+ T-lymphocytes were observed in exposed workers relative to controls. The number of CD57+CD16+ NK cells was observed to be inversely related to HgU levels.
Non-statistically significant findings:	No significant associations between exposure or HgU levels and other T-cell types, B-cells, or serum immunoglobulin levels were observed.
Dose response presence/absence:	
Biases identified by the authors:	Smoking and age were also found to affect T-cell counts
Assumptions/limitations of the study:	T-cell apoptosis was not monitored to assess whether declined counts are attributable to this mechanism.
Conclusions:	Number of CD4+45RA+ T lymphocytes and CD57+CD16+NK cells appeared to be inversely affected by exposure in workers with a mean HgU levels of 45 μg/L.
Reviewer Comments:	Method of urine collection not clear.

Information for Dose Response Assessment

All workers had been exposed for 4-62 months (mean 31). The mean HgU level was 44.8 μg/l (range 1.8-163.5), and the air TWA was 0.0041 mg/m^3. It is not clear how the urine samples were collected and the results were not corrected for creatinine, so the most reliable exposure estimate is the TWA value. This study is included in the dose-response assessment. It is not clear that the changes observed represent a clinically significant adverse effect and therefore will be considered a LOEL.

Epidemiological Study Critical Evaluation Form

Reference:	Perlingeiro, R.C.R. and M.L.S. Queiroz. 1995. Measurement of the respiratory burst and chemotaxis in polymorphonuclear leukocytes from mercury-exposed workers. Hum Exper Toxicol 14: 281-286.
Toxicological Endpoint:	Immunological

Criteria	
Peer reviewed:	Yes
Type of study:	
Population(s) studied:	Occupational: mercury producing plant
Case identification/definition	
Sample size:	48
Stratification (age, sex, etc.):	None
Control identification/definition	
Sample size:	48
Matching Criteria:	Age, gender and race.
Group selection method:	Control subjects had no history of mercury exposure and were chosen from blood donors arriving at the university hospital blood bank.
Data source for group information:	Medical examination, occupational history survey
Outcome(s) studied:	Neutrophil chemotaxis and neutrophil phagocytotic function (nitroblue test). A single evaluation was performed in the 48 exposed workers, and repeated after 6-months in 28 workers.
Exposure definition:	Average exposure of 8 months (range of 0.5 to 46).
Exposure measurement:	Mercury concentrations in urine (HgU)
Duration of exposure applicable to measurement (i.e. acute, chronic):	Subacute
Exposure levels:	In the first evaluation of all 48 workers, HgU levels ranged from 1.0 - 97.4 μg/g creatinine. In the 28 workers evaluated twice, the HgU range reported after the first and second evaluations, respectively, were 1.0 - 67.9 μg/g creatinine and 2.1 - 46.0 μg/g creatinine
Data adjustments:	
Results	
Relative Risk, Odd Ratio, Confidence Interval:	Not relevant
Statistics	
Procedures/tests:	Students t-test

Statistically significant findings:	Significant impairment of chemotaxis and nitroblue tetrazolium dye reduction were observed in blood samples of exposed workers relative to controls during the first evaluation. The level of neutrophil impairment did not return to normal after 6-months of reduced exposure
Non-statistically significant findings:	
Dose response presence/absence:	Not available
Biases identified by the authors:	Not available
Assumptions/limitations of the study:	Authors assume that impaired nitroblue tetrazolium dye reduction due, in part, to reduced myeloperoxidase levels and the formation of complexes between Hg to NADPH.
Conclusions:	Low-level Hg exposure (ie. HgU below the accepted TLV value of 50 μg/g creatinine may cause persistent impairment of neutrophil function.
Reviewer Comments	Morning spot-urine tests were used. Immunological mechanisms may also be of significance to renal endpoints; the authors note that Hg may induced renal damage throught the formation of immune completex that are filtered in the kidney, and induced immune complex nephritis.

Information for Dose-Response Assessment	The average duration of exposure was 8-months, but ranged from 0.5-46 months. It is not clear how many workers only experienced acute or short-term exposures to Hg. No air samples were taken. However, potentially irreversible adverse immunological effects were significantly associated with mean HgU levels of 24 μg/g creatinine at the time of exposure. Due to the effects observed in this study, it should be included in the dose-response assessment.

Epidemiological Study Critical Evaluation Form

Reference:	Queiroz, M. L. S., Perlingeiro, R. C. R., Dantas, D. C. M. Annichino Bizzacchi, J. M. and E.M. De Capitani. 1994. Immunoglobulin levels in workers exposed to inorganic mercury. Pharmacol. Toxicol. 74:72-75
Toxicological Endpoint:	Immunological
Criteria	
Peer reviewed:	Unknown
Type of study:	
Population(s) studied:	Occupational: mercury producing plant
Case identification/definition	
Sample size:	44
Stratification (age, sex, etc.):	None
Control identification/definition	
Sample size:	20
Matching Criteria:	Age, gender and race.
Group selection method:	Control subjects had no history of mercury exposure and were chosen from blood donors arriving at the university hospital blood bank.
Data source for group information:	Medical/neurological examination and occupational history survey.
Outcome(s) studied:	Serum IgG, IgA and IgM levels; prothrombin time, factor V, prealbumin and transaminase.
Exposure definition:	Average exposure period to mercury was 8 months (range of 3 to 46 months).
Exposure measurement:	Mercury concentrations in urine (HgU).
Duration of exposure applicable to measurement (i.e. acute, chronic):	
Exposure levels:	Mean HgU of 24.7 µg/g creatinine; majority of subjects below BEI of 50 µg/g creatinine.
Data adjustments:	
Results	
Relative Risk, Odd Ratio, Confidence Interval:	Not relevant.
Statistics	
Procedures/tests:	Unpaired Student's t-test: comparison of results from groups. Paired t-test: examine differences between the two evaluations performed in the 16 workers remaining in the plant during the 6 months of study. Pearson correlation coefficient: association between variables.

Statistically significant findings:	Significantly increased levels of IgG, IgA and IgM were observed in exposed workers relative to controls within the first 6-months following exposure.
Non-statistically significant findings:	Significant differences in levels of IgG, IgA and IgM were not observed in exposed workers after 6-months. No correlation between exposure duration, HgU or immunoglobulin levels were observed. No hematological abnormalities or signs of micromercurialism were observed.
Dose response presence/absence:	No correlation between exposure duration and immunological levels observed.
Biases identified by the authors:	Not identified
Assumptions/limitations of the study:	Mercury exposures were assumed to decrease in the plant due to improved hygiene practices.
Conclusions:	Exposures associated with HgU levels below acceptable limits may induce humoural immunological stimulation, but does not appear to be associated with hematological abnormalities or micromercurialism.
Reviewer Comments	Spot urine samples taken at time of blood sampling (early morning).

Information for Dose-Response Assessment	Average Hg exposure may be classified as chronic, as exposures ranged from 3-46 months. HgU results also appear to be reliable. This study suggests that potentially irreversible immunological effects may result from low-level Hg exposures, even after HgU levels have returned to normal and Hg exposure is reduced. Although the dose-response relationship is not clear, this study provides useful information regarding potentially irreversible low-level effects and should be included in the current assessment.