Epidemiological Study Critical Evaluation Form

Reference:	Aydin, N., Karaoglanoglu, S., Yigit, A., Keles, M.S., Kirpinar, I., and N. Seven. 2003. Neuropsychological effects of low mercury exposure in dental staff in Erzurum, Turkey. Int. Dent. J. 53: 85-91.
Toxicological Endpoint:	Neurological

Criteria	**Evaluation**
Peer reviewed:	Yes
Type of study:	Cohort
Population(s) studied:	Occupational: Turkish Dental Staff
Case identification/definition	
Sample size:	43 (33 dentists, 6 dental nurses and 4 dental technicians from 5 dental clinics; 23 males and 20 females; average exposure of 10 years with a range of 4 to 27 years).
Stratification (age, sex, etc.):	Occupation (dentist vs. nurse vs. technician and private vs. public), age, sex, education, number of amalgam surfaces, alcohol use, number of fish meals, smoking habits and neuropsychological test results.
Control identification/definition	
Sample size:	43 (34 physicians, 5 nurses and 4 health technicians)
Matching Criteria:	Similar to exposed group in age, gender, education and number of amalgam restorations in the mouth.
Group selection method:	Meeting of inclusion criteria and completion of a questionnaire.
Data source for group information:	Questionnaire.
Outcome(s) studied:	Neuropsychological tests: Wechsler Memory Scale-Revised (WMS-R) and Verbal Test of Memory Processes (VTMP) Self administered questionnaires: Symptom Checklist-90-Revised (SCL-90-R) and Beck Depression Inventory (BDI)
Exposure definition:	Inhalation exposure as a result of working daily with dental amalgam daily.
Exposure measurement:	Mercury concentrations in blood (HgB) and in morning urine sample (HgU).
Duration of exposure applicable to measurement (i.e. acute, chronic):	Author indicates urinary mercury has a half life of 40 to 80 days, lending to a measurements reflective of a subchronic exposure. However, all dental staff participating in the study have had chronic exposures.
Exposure levels:	Blood: average mercury concentration: 2.18 and 1.50 nmol/L in dental staff and controls, respectively. Urine: average mercury concentration: 1.17 and 0.64 nmol/L in dental staff and controls, respectively.
Data adjustments:	None

Results	
Relative Risk, Odd Ratio, Confidence Interval:	Not relevant
Statistics	
Procedures/tests:	Student t-test: group differences in background data, mercury levels in blood and urine and effect parameters Spearman's correlation coefficient: relationship between mercury levels in blood and urine and the neuropsychological test scores, number of amalgam restorations and duration of working time with amalgam. Stepwise regression analysis (backward procedure): associations between neuropsychological test results and education, gender, age, alcohol, fish consumption, current smoking habits. Two-tailed p-values provided. Calculated with data package SPSS 10.0.
Statistically significant findings:	Dental staff had a higher concentration of HgB and HgU than control group. HgU and HgB showed a significant positive correlation in the total group ($r=0.756$ $p<0.01$). HgU inversely related to logical memory I ($r=-0.237$, $p<0.05$) and logical memory II ($r=-0.221$, $p<0.05$) (WMS-R tests) and with total retention ($r=-0.210$, $p<0.05$) (a VTMP test). HgU were positively associated with anxiety ($r=0.217$, $p<0.05$) and psychoticism ($r=0.220$, $p<0.05$) (SCL-90-R). WMS-R test: statistically significant difference between dental and controls for logical memory I and logical memory II ($p<0.001$). Digit repetition and visual reproduction were negatively correlated with age. Logical memory was positively correlated with education years. VTMP: Immediate memory, words remembered trials, reaching the criteria and free delayed recall were positively correlated with education years. Total retention and words remembered trials were negatively correlated with age. SCL-90-R: dental staff showed statistically higher scores than the controls on Global Severity Index, Positive Symptom Total Index, Positive Symptom Distress Index, Somatisation, Obsessive-compulsive, anxiety, hostility and psychoticism. Current smoking habits was positively correlated with immediate memory.

Non-statistically significant findings:	No significant correlation between age, sex, occupation (private/public) and number of fillings in one's mouth of the dentists and HgB or HgU. No correlation with duration of working time (years) with amalgam or working area with HgB or HgU. WMS-R test: no significant difference between dental staff and controls for attention and visual memory test. VTMP: no significant difference between dental staff and controls. SCL-90-R: no significant difference between dental staff and controls on interpersonal sensitivity, depression, phobic anxiety and paranoid ideation. No relationship between neuropsychological tests and gender, alcohol and fish consumption.
Dose response presence/absence:	No association found between exposure years and mercury levels.
Biases identified by the authors:	Providing information about exposure to mercury may have led to worry by dental staff which in turn may have led to high scores in the self-reported questionnaire. Person who applied the neuropsychological tests was aware of which group the participants belonged to (i.e. was not blind to the subjects).
Assumptions/limitations of the study:	No exposure years-mercury level relationship was identified. Given the low dose - long term exposure of the dentists, it is considered that the urinary mercury output would be in a steady state condition and that the findings represent long-term consequences of low mercury exposure.
Conclusions:	Low-level chronic mercury exposures may lead to decreased memory performance and increased anxiety and psychoticism. HgU associated with decreased performance on logical memory and total retention and positively associated with anxiety and psychoticism. No correlation found between HgB and HgU and the duration of exposure.
Reviewer Comments	Morning urine samples collected and adjusted with creatinine.

Information for Dose-Response Assessment	This study has not been included in the dose-response assessment based on the biases identified by the author. The information provided to the dental staff may have led to the observed increase in anxiety and to the decreased memory performance.

Epidemiological Study Critical Evaluation Form

Reference:	Bittner, A.C. Jr., Echeverria, D., Woods, J.S., Aposhian, H.V., Naleway, C., Martin, M.D., Mahurin, R.K., Heyer, N.J., and M. Cianciola. 1998. Behavioural effects of low-level exposure to Hg° among dental professionals: A cross-study evaluation of psychomotor effects. Neurotoxicol. Teratol. 20(4): 429 – 439.
Toxicological Endpoint:	Neurological

Criteria	
Peer reviewed:	Yes
Type of study:	Cross-sectional
Population(s) studied:	Occupational: dental professionals
Case identification/definition	
Sample size:	Pooling of populations from six studies where n = 33, 28, 49, 75, 25 and 20. The six studies addressed included psychomotor assessments and were administered by the authors or their colleagues. (Note: not all studies addressed all outcomes considered in this cross-sectional study). A total of 230 subjects were included in the current study.
Stratification (age, sex, etc.):	Mean age varied from 46 to 53 (with standard deviations of 9 to 14). Six studies included predominantly males, with a total of 81% male participants overall.
Control identification/definition	No control group used. Exposure gradient studied instead.
Sample size:	NA
Matching Criteria:	NA
Group selection method:	Group selection method varied for the studies addressed. Four of the studies (American Dental Association (ADA), 1991, 1992, 1993 and 1995) used participants who attended the ADA annual sessions.
Data source for group information:	Results and records of previously conducted studies in populations of dental professionals were used to obtain information. During these studies, information was collected with medical and work history questionnaires, and various behavioural tests.
Outcome(s) studied:	Psychomotor function: finger tapping, intentional hand steadiness test (IHST), one-hole test, NES simple reaction test and hand tremor.
Exposure definition:	Inhalation exposure as a result of working daily with dental amalgam.
Exposure measurement:	Mercury concentration in urine (HgU).
Duration of exposure applicable to measurement (i.e. acute, chronic):	Chronic occupational exposure.
Exposure levels:	All individuals included in the study had HgU levels ≤ 55 µg/L.

Data adjustments:	Individuals with history of neurologic disorders, hypertension, diabetes, pharmaceutical use (not defined) were excluded to eliminate the potential for confounding results.
Results	
Relative Risk, Odd Ratio, Confidence Interval:	Not relevant
Statistics	
Procedures/tests:	Multivariate analyses; Principle Factor Analyses (PFA); Spearman-Brown equation and Minres regression analysis.
Statistically significant findings:	Significant relationship between IHST general factor variable and log HgU levels, age, gender and drink frequency. Significant relationship between increasing log HgU with decreasing IHST performance. Significant relationship between finger tapping general factor with age, gender, and drink frequency. Correlation between One-Hole test results and finger tapping scores, and One-Hole test results and tremor summary scores.
Non-statistically significant findings:	Non-significant relationships between: finger tapping and log HgU levels; performance in One-Hole test and log HgU levels; HgU and Simple Reaction Time; Simple Reaction Time with the variables age, gender and drink frequency; and, hand tremor and log HgU levels.
Dose response presence/absence:	Present for decreasing IHST score.
Biases identified by the authors:	None
Assumptions/limitations of the study:	The five psychomotor tests used appear to assess different psychomotor tendencies. However, only one test was found to correlate with Hg exposure.
Conclusions:	The Intentional Hand Steadiness Test (IHST) factor summary score is a relevant test for evaluating psychomotor performance in dental professionals.
Reviewer Comments	Although subjects had HgU levels ≤55 µg/L, several subjects were below 20 µg/L,however this proportion isn't clear.

Information for Dose-Response Assessment	At HgU concentrations of ≤55 µg/L, psychomotor performance effects were identified (i.e. in the IHST). It should be noted that an undescribed proportion of the workers studied had HgU levels below 20 µg/L. Exposures correlating to HgU levels much less than 55 µg/L must be considered. It must be noted that HgU levels were not adjusted for creatinine, making direct comparison with other study results more difficult. This study should not be used further in the current assessment.

Epidemiological Study Critical Evaluation Form

Reference:	Boogaard, P.J., Houtsma, A.T.A.J., Journee, H.L., and N.J. van Sittert. 1996. Effects of exposure to elemental mercury on the nervous system and the kidneys of workers producing natural gas. Arch. Environ. Health. 51(2): 108-115.
Toxicological Endpoint:	Renal and Neurological

Criteria	
Peer reviewed:	Unknown
Type of study:	Cohort
Population(s) studied:	Occupational: Employees of an industrial cleaning company that are involved in cleaning activities at gas-production sites.
Case identification/definition	
Sample size:	High-exposure group:18; first low-exposure group: 9; second low exposure-group: 13. Note that the first and second low exposure group were pooled into a single study group.
Stratification (age, sex, etc.):	Data was stratified according to exposure group; age; mean underarm length; smoking habits; alcohol, fish and coffee consumption; recent dental restorations; number of amalgam fillings and medication use.
Control identification/definition	
Sample size:	19
Matching Criteria:	Control subjects were matched well for number of subjects, underarm length, number of smokers and smoking habits, number of alcohol users and alcohol consumption, number of fish eaters and fish consumption, number of coffee drinkers and coffee consumption, number of amalgam fillings and number of medication users. Not matched well for age and number of persons with recent dental restoration.
Group selection method:	Exposure groups participants all work within a gas-production site in The Netherlands. High-exposure group were involved regularly in cleaning activities, LOW-1 had potential chronic exposure to low concentrations of Hg and LOW-2 were exposed incidentally to low concentrations of Hg. Control workers were selected from areas of the plant without Hg exposures.
Data source for group information:	Self-administered questionnaire, occupational history records and historical exposure records.

Outcome(s) studied:	Neurological tests: motor nerve conduction velocity (MNCV), EMGs of forearm at rest (REST-R and REST-L for the right and left arms), stretched (ACT-R and ACT-L) and with bowed arms at the sustained end of the finger-nose test with closed eyes (INT-R and INT-L). Biochemical tests: albumin, β2M, NAG and total protein.
Exposure definition:	Occupational exposures in workers at a natural gas plant in the Netherlands.
Exposure measurement:	Mercury concentrations in blood (HgB), in urine (HgU) (collected over 5 days) and in air during the study. Stationary air monitoring was conducted on 2 days at 15 different locations. Personal air measurements were collected from 10 individuals, 9 from the high group and 1 from the LOW group. Historical mercury concentrations in urine were also obtained from urinalysis records for the production site.
Duration of exposure applicable to measurement (i.e. acute, chronic):	Chronic
Exposure levels:	Urine (present): mean mercury concentrations: 23.7, 4.1 and 2.4 µg/g in the high, low and control groups, respectively. Urine (historical): mean mercury concentrations are 41.8, 17.3 and 3.6 µg/L in the high, low and control groups, respectively. Blood: present mercury concentrations: 3.5, 1.5 and 2.2 µg/L in the high, low and control groups, respectively. Air: Stationary samples ranged from 10 to 1500 $\mu g/m^3$ (median = 67 $\mu g/m^3$) in areas of anticipated exposure and 0 to 6 $\mu g/m^3$ at locations with no or little exposure. From the personal monitors the 8-h time-weighted average exposure ranged from 33 to 781 $\mu g/m^3$ (median of 88 $\mu g/m^3$).
Data adjustments:	LOW-1 and LOW-2 study group were pooled into a single study group as all metal, biochemical and neurological determination did not differ significantly. When appropriate, corrections were made for age or dentistry. The distribution of potential confounders were compared between groups: fish, alcohol and coffee consumption, smoking habits, recent dental restorations and medication use
Results	
Relative Risk, Odd Ratio, Confidence Interval:	Not relevant.
Statistics	

Procedures/tests:	Fisher's two tailed exact test for discrete variables and Wilcoxon's rank-sum test for continuous variables: comparison of possible confounders in the study and control groups *F* test with stepwise regression analysis: neurological and biochemical variables and the influence of possible confounders on the biochemical and neurological variables. Multivariate regression analysis: influence of mercury exposure on neurological and biochemical variables and on the results of the variables of the entire population with HgU and HgB as independent variables. Use of SAS statistical software package with a level of significance <0.5.
Statistically significant findings:	HgB in high-exposure group was significantly higher than HgB in low-exposure group. HgU present and historical were significantly higher than the low-exposure or control group. β2M and NAG were significantly increased in the high-exposure group over the low-exposure group, however, the individual results of the workers in both groups were within the 95% confidence interval of workers who are not exposed occupationally. Correlation with NAG and HgU values (Pearson correlation coefficient = 0.53, $p<0.0001$).
Non-statistically significant findings:	No significant correlations between HgU and renal parameters, other than NAG. No correlation between NAG and duration of exposure. No statistically significant differences for any of the biochemical test between the low-exposure and control groups. No statistically significant difference among the three study group for any the neurological tests. No statistically significant correlations found between the results of the neurological parameters and either the present or the historical biological monitoring parameters.
Dose response presence/absence:	Results indicate that higher levels of exposure are associated with higher levels of the renal biomarkers, however, no dose-response relationship was observed between mercury exposure and either the development of renal dysfunction or neurological effects.
Biases identified by the authors:	The workers included in the present study may have been exposed to Hg intermittently, rather than continually, which may have affected the overall exposure of the subjects.

Assumptions/limitations of the study:	The exposure frequency and duration are not provided for exposure groups. The workers included in the present study may have been exposed to Hg intermittently, rather than continually, which may have affected the overall exposure of the subjects.
Conclusions:	No neurological effects were identified. An increase in NAG was observed in high-exposure group. the author indicated that the increase in NAG may be a transient effect that is related to recent exposure and that such an increase is not considered an indicator of persistent renal alterations or renal dysfunction.
Reviewer comments:	The increase in NAG is considered relevant in developing a safe Hg level for chronic exposures.

Information for Dose-Response Assessment	No clinically significant effects were associated with current or historical exposure. However, β2M and NAG were significantly increased in the high-exposure group. A significant correlation between HgU and NAG was identified. HgU concentrations were chosen as an indicator of exposure as 1) they were correlated with an observed effect and 2) air measurements were performed "occassionally" and it is unclear how appropriate these measurements are in describing exposure. This study is included for consideration in the dose response assessment.

Epidemiological Study Critical Evaluation Form

Reference:	Cardenas, A., Roels, H., Bernard, A.M., Barbon, R., Buchet, J.P., Lauwerys, R.R., Rosello, J., Hotter, G., Mutti, A., Franchini, I., Fels, L.M., Stolte, H., De Broe, M.E., Nuyts, G.D., Taylor, S.A., and R.G. Price. 1993. Markers of early renal changes induced by industrial pollutants. I. Application to workers exposed to mercury vapor. Br J Ind Med 50: 17-27.
Toxicological Endpoint:	Renal

Criteria	
Peer reviewed:	Unknown
Type of study:	Cohort
Population(s) studied:	Occupational: Belgian chloroalkali plant workers
Case identification/definition	
Sample size:	44
Stratification (age, sex, etc.):	None
Control identification/definition	
Sample size:	49
Matching criteria:	Sex
Group selection method:	Exposed and control workers were examined. Exposed group consisted of male workers exposed to mercury vapour in a chloralkali plant for at least one year. Control group worked in the same plant but was not exposed to Hg. Participants met the following criteria: absence of kidney disease or diseases that could impair renal function; did not consume drugs with potential nephrotoxicities; demonstrated concentrations of HgU < (controls) or > (exposed) than 5 µg/g; demonstrated urinary creatinine concentrations between 0.3 and 4 g/L.
Data source for group information:	Questionnaires and biological monitoring data.
Outcome(s) studied:	Functional markers: creatinine, β2-microglobulin (β2M) in serum and urinary proteins of low or high molecular weight. Cytotoxicity markers: tubular antigens and enzymes in urine. Biochemical markers: eicosanoids, fibronectin, kallikrein activity, sialic acid and glycosaminoglycans in urine and red blood cell membrane negative charges.
Exposure definition:	Occupation exposure from chloralkali plant, over a duration of exposure between 1.5 to 25 years (average of 11 years).
Exposure measurement:	Mercury concentrations in blood and urine.
Duration of exposure applicable to measurement (i.e. acute, chronic):	Chronic
Exposure levels:	Urine: 21.9 and 1.6 µg/g creatinine in exposed and control groups, respectively. Blood: 7.2 and 1.0 µg/L in exposed and control groups, respectively.

Data adjustments:	Parameters measured in serum (except B2M and creatinine), whole blood and urine were normalised by log transformation.
Results	
Relative Risk, Odd Ratio, Confidence Interval:	Not relevant
Statistics	
Procedures/tests:	Stepwise Regression: assess influence of age Multivariate regression analysis: standardized for age and carried out on whole population with crt-U, BMI, smoking habits, alcohol consumption and HgB or HgU as possible determinants. Effect of duration of exposure tested by adding it as an independent variable in analysis of the exposed group. Pearson's correlation: assess association between some variables Student's t-test for unpaired data and Duncan's test: compare group means Fisher's exact test: prevalence of abnormal values Logistic regression model: relations between frequency of abnormal values of renal markers and HgB or HgU. All analyses performed with SAS with a statistical significance of $p \leq 0.05$.
Statistically significant findings:	Exposed group has a significantly higher urinary excretion of THG, tubular antigens (BB50, BBA, HF5, IAP) and a significant reduction in the excretion of β_2M, GAG, PGE_2, PGF_2 and TXB_2 and in urinary pH. All urinary variables were positively correlated with creatinine-adjusted urine. Significant increase in mean urinary NAG activity and a decrease in urinary kallikrein activity were observed in the workers exposed to the highest levels of Hg.
Non-statistically significant findings:	No significant association between renal effects and the duration of exposure were observed
Dose response presence/absence:	Renal changes were generally dose related. Most of the effects reached statistical significance at HgU higher than 50 µg/g creatinine.
Biases identified by the authors:	
Assumptions/limitations of the study:	
Conclusions:	An increase in protein excretion was not identified within the exposed group. Other signs of renal cytotoxicity and biochemical alterations were identified. Increased urinary excretion of THG appears to be an early renal effects associated with exposure to Hg vapour.

Reviewer comments:	Spot-urine test used to determine HgU. Creatinine adjusted HgU results. Physiological function of THG is uncertain, according to authors. Increased excretion could indicate injury to epithelial cells of the thick ascending limb of the Loop of Henle. Increased urinary excretion of BB50, BBA, HF5 and IAP likely reflect damage to proximal tubular cells. Authors described a potential threshold level for renal effects of 50 µg/g HgU creatinine, based on renal changes. Renal effects may be reversible and caused only by recent exposure. Cadmium and lead were also measured during the study. While lead levels were not different between the control group and the exposed group, the cadmium levels in urine (when adjusted for creatinine) were significantly different. Cadmium levels in urine were 0.31 µg/g creatinine in the control group and 0.44 µg/g creatinine in the exposed group. Cadmium exposure also leads to nephrotoxic effects. However, in a similiar study conducted by the authors it was found that the threshold for biochemical changes is around 2 µg Cd/g creatinine. In the study addressed here, it was identified through monitoring data that none of the controls or exposed group had cadmium levels in urine greater than 2 µg Cd/g creatinine. As such, although the cadmium levels in urine were greater in the exposed group, the level of cadmium is not considered to be high enough to effect the results of the study

Information for Dose-Response Assessment	Indicators of chronic renal toxicity were clinically significant with HgU levels > 50 µg/g creatinine. A significant increase in abnormal GAG and PGE_2 results occurred when HgU exceeded 35 µg/g and HgB exceeded 4.3 µg/l. A statistically significant association between the prevalence of reduced GAG and HgU and between the prevelance of decreased PGE_2 and HgB were identified. Although no air levels were monitored, the long duration of exposure and number of workers involved in the study make it useful to the dose-response assessment. No information is provided by the author to suggest which exposure measurement (i.e. HgU or HgB) is most appropriate to use in the dose-response assessment. HgU has been chosen as an indicator of Hg exposure as its concentration is considered more representative of chronic Hg exposure than HgB.

Epidemiological Study Critical Evaluation Form

Reference:	Chang, Y.C., Yeh, C.Y, and J.D. Wang. 1995. Subclinical neurotoxicity of mercury vapor revealed by a multimodality evoked potential study of chloralkali workers. Am J Ind Med 27: 271-279.
Toxicological Endpoint:	Neurological

Criteria	
Peer reviewed:	Yes
Type of study:	
Population(s) studied:	Occupational: chloralkali factory
Case identification/definition	
Sample size:	26 (10 in high exposure group, 5 in medium exposure group, 11 in low exposure group)
Stratification (age, sex, etc.):	None
Control identification/definition	
Sample size:	26
Matching Criteria:	Controls were matched for age and body height for the somatosensory stimulation evoked potentials (SEP) study.
Group selection method:	Participants in the study were previously employed at a chloralkali factory in Taipei that closed in 1989. High exposure group worked with the electrolysis process and close to the electrolysis bath. Medium exposure workers were in-plant workers who came into contact with elemental mercury occasionally and low exposure workers did not participate directly in the process of production.
Data source for group information:	Questionnaire, biological assessments conducted on the factory workers when the factory closed.
Outcome(s) studied:	Biological Hg levels; Neurological effects including: Pattern visual evoked potentials (pVEPs), brainstem auditory evoked potentials (BAEP) and somatosensory stimulation evoked potentials (SEP).
Exposure definition:	Retrospectively judged from each individual working history. Average of 12 years (range of 9 months to 26 years) of work at factory.
Exposure measurement:	Blood, urine and hair samples were collected, and neurological tests performed 40 to 70 days after the factory closed.
Duration of exposure applicable to measurement (i.e. acute, chronic):	Chronic

Exposure levels:	Urine: average of 45.6, 18.1 and 16.8 µg/L in high, medium and low exposure groups respectively. Blood: 3.0, 2.7 and 2.7 µg/dL in high, medium and low exposure groups respectively. Hair: 53.9, 9.7 and 4.9 in high, medium and low exposure groups respectively.
Data adjustments:	Data regarding somatosensory evoked potential (EP) were calculated and analyzed separately from the right and left side to minimize bias.
Results	
Relative Risk, Odd Ratio, Confidence Interval:	NA
Statistics	
Procedures/tests:	Paired t-test - significance of latency differences in EP findings; Mann-Whitney test - significance of amplitude difference; one-way ANOVA - significance of EP results; Scheffes procedure - evaluation of any discrepancies in results.
Statistically significant findings:	pVEPs: Mean N1-P1 interpeak amplitude was significantly larger in mercury group as a whole and in the high-exposure group than in the controls. BAEP: Significant delay of wave V latency leading to a prolongation of I-V interpeak latencies in the high-exposure group compared to controls. SEP: Significant prolonged scalp SEP latency and CCT in the high-exposure group compared to controls.
Non-statistically significant findings:	pVEPs: No significant difference of N1, P1 or N2 peak latency between exposure groups and control group. BAEP: No significant difference in wave I and wave III latencies between exposure groups and controls. SEP: no significant difference in brachial NAP and neck SEP latencies between exposure groups and controls. No significant neurological abnormalities were observed in routine neurological examinations.
Dose response presence/absence:	No significant correlation between EP abnormalities and body mercury levels. However, changes were mainly seen in the high-exposure group.
Biases identified by the authors:	
Assumptions/limitations of the study:	The study was conducted 40 days after the workers had left their jobs. As a result, the mercury levels are underestimates of occupational exposure levels.
Conclusions:	Chronic Hg vapour exposure was associated with neurological effects (EP).

Comments	24-hour urine collection was used. Authors note that since the study was conducted at least 40-days post-exposure, the Hg levels detected in the workers must be underestimates of actual exposures. Some question as to how relevant EP findings are, due to conflicting results from various studies.

Information for Dose-Response Assessment	The exposure measurements were collected 40 days after exposure ended. This time period is roughly equivalent to the estimated half-life of HgU excretion and is much longer than the half-life of HgB excretion. The HgU and HgB levels in this study, therefore, are not very predictive of the workers' actual exposures. Additionally, adverse effects may have initially been present in some subjects during the time of exposure, but reversed after the exposure ceased. This study should therefore not be included in the dose-response assessment.

Epidemiological Study Critical Evaluation Form

Reference:	Discalzi, G., Fabbro, D., Meliga, F., Mocellini, A., and F. Capellaro. 1993. Effects of occupational exposure to mercury and lead on brainstem auditory evoked potentials. Int. J. Psychophysiol. 14: 21-25.
Toxicological Endpoint:	Neurological

Criteria	
Peer reviewed:	Unknown
Type of study:	Cohort
Population(s) studied:	Occupational: employees at metallic bowl factories
Case identification/definition	
Sample size:	8
Stratification (age, sex, etc.):	None
Control identification/definition	
Sample size:	8
Matching Criteria:	Age and sex
Group selection method:	Subjects exposed to inorganic mercury in metallic bowl factories. Control subjects were never exposed to neurotoxic substances, as indicated in a self-report.
Data source for group information:	Controls provided a self-report regarding exposure.
Outcome(s) studied:	Brainstem auditory evoked potentials (BAEPs)
Exposure definition:	Average duration of mercury exposure was 11.7 (S.D. of 8) years.
Exposure measurement:	Mercury concentration in urine (HgU) measured at the end of the work shift.
Duration of exposure applicable to measurement (i.e. acute, chronic):	
Exposure levels:	Mean HgU level was 325 µg/g creatinine.
Data adjustments:	None identified.
Results	
Relative Risk, Odd Ratio, Confidence Interval:	Not relevant
Statistics	
Procedures/tests:	t-test for paired data, analysis of variance and linear regression
Statistically significant findings:	BAEPs I-V interpeak latencies were significantly different between exposed group and controls.
Non-statistically significant findings:	No significant correlations found between electrophysiological data, duration of exposure and HgU levels.

Dose response presence/absence:	Not defined.
Biases identified by the authors:	Small group of participants in the exposure group prevented the ability to draw conclusions about the dose-response function.
Assumptions/limitations of the study:	Small group of participants in the exposure group prevented the ability to draw conclusions about the dose-response function.
Conclusions:	Workers exposed to Hg vapours demonstrated a slowing and attenuation of cerebral electric activity in the occipital region. Evoked potentials appear to be sensitive to CNS impairment at the subclinical level.
Reviewer Comments	HgU sample taken at end of workday, on day before neuro test.

Information for Dose-Response Assessment	Mean HgU level was found to be 325 μg/g creatinine, with the average duration of exposure being 11.7 years. Single HgU samples were taken at the end of a workshift. The diurnal excretion of HgU is known to vary, and to be greater in the morning. The HgU results in this study may not be reliable due to the small number of samples and the timing of the collection. Although the workers appeared to have been chronically exposed, the level of this exposure is not known. This study does not appear to provide information relating to dose-response or persistent effects. For these reason, combined with the potential discrepancies in HgU levels, this study should not be included in the dose-response assessment.

Epidemiological Study Critical Evaluation Form

Reference:	Echeverria, D., Heyer, N., Martin, M., Naleway, C., Woods, J. and A. Bittner. 1995. Behavioral effects of low-level exposure to elemental Hg° among dentists. Neurotoxicol. Teratol. 17:161-168.
Toxicological Endpoint:	Neurological

Criteria	
Peer reviewed:	Yes
Type of study:	Cross-sectional
Population(s) studied:	
Case identification/definition	
Sample size:	19
Stratification (age, sex, etc.):	Age, race, gender, education, medical history of neurologic disorders, hypertension, diabetes and pharmaceutical use.
Control identification/definition	
Sample size:	20
Matching Criteria:	Randomly selected from population of dentists with no detectable HgU.
Group selection method:	Dentists with spot-sample HgU results > 19 µg/L were asked to participate in study.
Data source for group information:	Symptom and medical questionnaire, Profile of Mood Scales, behavioural tests and biological samples.
Outcome(s) studied:	Behavioural effects: digit-span, symbol-digit substitution, simple reaction time, multitasking ability, vocabulary, and One-Hole test.
Exposure definition:	Groups of dentists exposed and unexposed to Hg vapour were compared.
Exposure measurement:	HgU spot sample
Duration of exposure applicable to measurement (i.e. acute, chronic):	Subjects likely have experienced chronic exposure due to their occupation. It is possible some of the subjects had acute exposure.
Exposure levels:	Dentists in the exposed group selected to have HgU levels greater or equal to 19 µg/L.
Data adjustments:	Age in years, age-squared, gender, race, alcohol consumption/use, history of neurological disease, nitrous oxide use were evaluated as potential confounders. Variables found to have outlier results that could affect the analysis or were observed to be too divergent from normal distributions were log transformed so that they did not affect the analyses.
Results	
Relative Risk, Odd Ratio, Confidence Interval:	NA

Statistics	
Procedures/tests:	Multivariate regression; one-side p value; Bonferroni test and sums of ranked scores.
Statistically significant findings:	Significant relationship between HgU levels and poor mental concentration, emotional lability, somatosensory irritation, mood scores, vocabulary. Significant association between coproporphyrin (one of 3 urinary porphyrins altered by Hg exposure) associated with abnormalities in digit span and simple reaction time.
Non-statistically significant findings:	No significant association between total symptoms and any exposure measurement (including HgU) . Results of cognitive and motor function tests.
Dose response presence/absence:	Dose-response relationship observed.
Biases identified by the authors:	Differences in nitrous oxide use by dentists may have contributed to the observation of lesser differences in performance between exposure groups. The use of spot-tests rather than 24-hour collection and potential selection bias may have affected the selection of subjects for the study - the potential effects on the results of this is unknown.
Assumptions/limitations of the study:	Sample size of exposed group was relatively small, and made it difficult for authors to control all potential confounders.
Conclusions:	Adverse preclinical effects were observed in a population of dentists exposed to low levels of Hg vapour. Mean HgU of 36 µg/L in the group of exposed dentists, and no detectable HgU detected in control dentists. In general, HgU levels associated with mood and symptom measures, and coproporphyrin levels were more closely associated with impairment of cognitive function. Precoproporyhrin may be the best biomarker of Hg exposure as it is usually found at higher levels and is less variable.
Reviewer comments	More study is needed to determine the threshold of adverse biologic effects. Study used urine spot tests, but is not clear when in relation to the workshift these samples were taken.

Information for Dose-Response Assessment	Significant dose-response relationship was observed in this study, with the mean observed threshold for these effects being HgU levels of 36 µg/L. It must be noted that HgU levels were not adjusted for creatinine, making direct comparison with other study results more difficult. Air samples were not taken in the dental offices, so the actual exposures levels are unknown. Furthermore, the exposure duration is not very clear. This study should not be included in the dose-response assessment.

Epidemiological Study Critical Evaluation Form

Reference:	Echeverria, D., Aposhian, H.V., Woods, J.S., Heyer, N.J., Aposhian, M.M., Bittner, A.C.Jr., Mahurin, R.K., and M. Cianciola. 1998. Neurobehavioural effects from exposure to dental amalgam Hg(0): New distinctions between recent exposure and Hg body burden. FASEB 12(11): 971 – 980.
Toxicological Endpoint:	Neurological

Criteria	
Peer reviewed:	Unknown
Type of study:	
Population(s) studied:	Occupational: dentists and dental staff
Case identification/definition	
Sample size:	47
Stratification (age, sex, etc.):	None
Control identification/definition	
Sample size:	None
Matching Criteria:	Not applicable.
Group selection method:	49 subjects (dentists and dental assistants) were asked to participate. After medical screening, based on a pretest questionnaire, 2 subjects were eliminated.
Data source for group information:	Questionnaires were used to obtain information about medical and occupational histories and work practices.
Outcome(s) studied:	Symptoms, profile of mood states, hand steadiness, simple reaction time, finger tapping NES, tremor analysis test system (acceleration finger tremor), one-hole pins, vocabulary NES, recognition memory test (for words), trailmaking A and B, visual retention test NES, switching task and symbol-digit NES.
Exposure definition:	Occupational: dentists and dental assistants
Exposure measurement:	Mercury concentration in urine (HgU) pre- and post-chelation (to evaluate recent exposure but not chronic body burden).
Duration of exposure applicable to measurement (i.e. acute, chronic):	Chronic
Exposure levels:	HgU levels of dentists and dental assistants studied did not differ between pre-and post-chelation samples. Mean pre-chelation results: 0.89 µg/L (dentists), 1.07 µg/L (dental assistants); mean post-chelation results: 10.08 µg/L (dentists), 8.07 µg/L (dental assistants).
Data adjustments:	
Results	
Relative Risk, Odd Ratio, Confidence Interval:	Not applicable

Statistics	
Procedures/tests:	Multiple regression analysis, Paired t-tests and Standardized beta coefficients.
Statistically significant findings:	Significant correlation between pre and post-chelation HgU levels. Significant association between prechelation HgU levels and: number of restorations/week, form of amalgam used, mask use, number of amalgam fillings. Significant associations between pre-chelation HgU and mood scales, and post-chelation HgU and persistent neurological symptoms (memory, headaches, lightheadedness, dizziness).
Non-statistically significant findings:	No significant association between Hg exposure and symbol-digit response. No effect on resting tremor was observed.
Dose response presence/absence:	No evidence of a threshold effect was evident, and the dose-response relationship demonstrated a log-linear trend. Statistically significant dose-response relationships were observed for pre-chelation HgU and post-chelation HgU.
Biases identified by the authors:	None
Assumptions/limitations of the study:	None
Conclusions:	There is evidence of associations of recent and chronic Hg exposure with distinct patterns of preclinical effects. Work-related and personal factors were found to be determinants of pre-chelation HgU levels. There is no evidence of an effect threshold in this study. Results suggest that the preclinical effects observed at low levels of Hg exposure may occur at the same time as more severe clinical effects. No evidence of an especially sensitive population was identified within the groups studied.
Reviewer Comments	Urine spot samples collected prechelation and postchelation.

Information for Dose-Response Assessment

Mean pre-chelation HgU results were found to be 0.89 µg/L (dentists), 1.07 µg/L (dental assistants), and all study subjects were reported to have been chronically exposed (although the duration is not clear). Significant differences in the incidence of neurological effects was observed between pre- and post-chelation assessments, indicating that significant clinical effects associated with Hg exposure were observed in the subjects before treatment. Information concerning exposure levels is limited to measurements of HgU. However, urine results were not adjusted for creatinine. Overall, this study is not particularly of value to the dose-response assessment due to lack of information regarding exposure and dose-response relationships.

Epidemiological Study Critical Evaluation Form

Reference:	Ellingsen, D.G., Efskind, J., Berg, K.N., Gaarder, P.I. , and Y. Thomassen. 2000. Renal and immunological markers for chloralkali workers with low exposure to mercury vapor. Scand J Work Environ Health 26(5): 427-435.
Toxicological Endpoint:	Renal and immunological
Criteria	
Peer reviewed:	Yes
Type of study:	Cross-sectional
Population(s) studied:	Occupational: chloralkali workers
Case identification/definition	
Sample size:	47
Stratification (age, sex, etc.):	None
Control identification/definition	
Sample size:	47
Matching Criteria:	Controls matched by age with exposed subjects
Group selection method:	Men with exposure to mercury vapour for at least 1 year in a contaminated area of a plant under study were eligible for inclusion in the exposure group. Control group included men employed by the same company at the same industrial complex and had no known current or past occupational exposure to mercury.
Data source for group information:	Medical examination, and interview emphasizing occupational and medical history, sociodemographic background and current alcohol consumption.
Outcome(s) studied:	Renal markers:urinary albumin (U-alb), β2-microglobulin in urine (β2M), alkaline phosphatase in urine (U-ALP), alanine aminopeptidase in urine (U-AAP), N-acetyl-β-D-glucosaminidase in urine (U-NAG), glycosaminoglycanes in urine (U-GAG), kallikrein in urine (U-Kal), glomerular basement membrane (anti-GBM). Immunological markers: antinuclear antibodies (ANA), autoantibodies to proteinase 3 in serum (anti-PR3), autoantibodies to myeloperoxidase in serum (anti-MPO), anit-PR3, immunoglobulin (IgE).
Exposure definition:	Occupational exposure in a mercury contaminated area of a chloralkali plant.

Exposure measurement:	Mercury concentration in urine and blood at the time of study and historical concentrations in urine obtained from routine measurements within the plant. Average exposure of 42 (range of 24.0 - 66.8) and 41.9 years (range of 23.3 - 64.2) among exposure and control groups, respectively.
Duration of exposure applicable to measurement (i.e. acute, chronic):	Chronic
Exposure levels:	During study: Average HgU = 5.9 nmol/mmol Cr, HgB total 43.5 nmol/L, HgBinorg(nmol/L) Mean 20.7 (range 2.5-65) Historical: Average HgU = 9.0 nmol/mmol Cr
Data adjustments:	HgU concentrations prior to 1982 were not corrected for creatinine. The mean urinary creatinine in 1982 and 1983 was used to correct the concentrations measured prior to 1982. Data was log-transformed when variable distribution had a skewness exceeding 2 or if differences to be compared had different variances (Levene's test).
Results	
Relative Risk, Odd Ratio, Confidence Interval:	Not Available
Statistics	
Procedures/tests:	Variance analysis: group comparisons Multiple linear regression analysis (backward procedure): association between effect variables, exposure measures and potential confounders (age, smoking habits, alcohol consumption, selenium in whole blood (B-Se), and selenium in urine (U-Se)).
Statistically significant findings:	U-NAG was statistically significantly higher in the exposed group than the reference group. U-NAG concentration was positively associated with HgU, Cum HgU/year and age in the regression analysis.
Non-statistically significant findings:	None
Dose response presence/absence:	Not applicable
Biases identified by the authors:	Smoking was found to be associated with lower tests scores in the Static Steadiness and Pegboard tests. An association was observed between the amount of tobacco smoked/week and results of the Static Steadiness test.
Assumptions/limitations of the study:	Mean HgU levels were calculated for each year, and cumulative exposure was determined by dividing this number by HgU by years of exposure. Cumulative HgU is therefore an estimate and not an actual test value.

Conclusions:	Chronic, low-level exposure to Hg induced adverse renal effects characterised by effects in kidney proximal tubule cells (NAG biomarkers). There was some evidence of immunological and inflammatory activity
Reviewer Comments:	HgU determined from spot-tests in morning. Recent urinary results corrected for creatinine. Cumulative index of exposure (Cum HgU) calculated based on worker's mean HgU for each annual quarter. Annual mean exposures were calculated, and from this Cum HgU was estimated. Workers also exposed to cadmium and selenium. Co-exposures to selenium and cadmium may have influenced observations, however, the effects of these substances on the results was considered during statistical analysis. Two morning urine spot-tests conducted for recent HgU exposures and were adjusted for creatinine during analysis. Historical HgU values were corrected by the authors for creatinine. Authors concluded that HgB measurements are not associated with U-NAG level and the HgB concentrations are more reflective of recent exposures.

Information for Dose-Response Assessment	A dose-response relationship between HgU levels and urinary NAG levels (renal biomarker) was observed. In actual study the mean HgU level in the exposed workers was 5.9 nmol/mmol creatinine (range 1.1-16.8), and all workers had been exposed to HgU for at least 1-year. In the historical portion of the study, the mean exposure duration was 13.3 years (range 2.8-34.5), with the mean cumulative HgU/year value calculated as 9 nmol/mmol creatinine/year, however NAG data was not available for this study group. This study provides a correlation between an HgU level and a renal effect (i.e. NAG biomarker), for which a dose-response relationship has been observed, and provides some useful information for the assessment. Based on the information, HgU concentrations will be used to estimate exposure levels in the dose-response assessment.

Epidemiological Study Critical Evaluation Form

Reference:	Ellingsen, D.G., Gaarder, P.I., and H. Kjuus. 1994. An immunological study of chloralkali workers previously exposed to mercury vapour. Apmis. 102:170-176.
Toxicological Endpoint:	Immunology

Criteria	
Peer reviewed:	Unknown
Type of study:	Cross-sectional
Population(s) studied:	Occupational: chloralkali workers
Case identification/definition	
Sample size:	51
Stratification (age, sex, etc.):	
Control identification/definition	
Sample size:	53
Matching Criteria:	Controls matched with exposed subjects by age
Group selection method:	Workers under the age of 66 exposed to Hg vapour for at least 1-year in a contaminated area of the plant were invited to participate.
Data source for group information:	Male workers at the plant had been routinely monitored for HgU levels since 1949. Occupational and medical history, socio-demographic information, and alcohol consumption information was obtained from interviews
Outcome(s) studied:	Immunological and neurological effects
Exposure definition:	Occupational exposure in a mercury contaminated area of a chloralkali plant
Exposure measurement:	Mercury concentrations in urine (HgU), blood (HgB), and cumulative HgU were assessed.
Duration of exposure applicable to measurement (i.e. acute, chronic):	Exposure was chronic, and historic. The mean duration of exposure was 7.9 years. Exposure ceased on average 12.3 years before this study commenced.
Exposure levels:	Mean current levels of HgU was 1.8 nmol/mmol creatinine in the exposed group and 1.3 nmol/mmol creatinine in the control group. Mean current levels of HgB in whole blood were 26.4 nmol/L in exposed subjects and 28.3 nmol/L in the control group.
Data adjustments:	Some exposed subjects excluded due to solvent exposure or alcohol abuse
Results	
Relative Risk, Odd Ratio, Confidence Interval:	Not applicable
Statistics	

Procedures/tests:	Non-parametric Mann-Whitney test; Spearman's rank correlation test; Fisher's test
Statistically significant findings:	Significant higher thyroglobin levels was observed in exposed subjects (9.4%) relative to controls (1.3%). No significant differences observed between the exposed and control groups were observed for immunological endpoints (autoantibodies, immunoglobulins, complement proteins). No anti-double strand DNA, anti-nucleolar, or anti-centromere antibodies were detected in exposed workers.
Non-statistically significant findings:	Non-significant increased levels of thyroid microsomal antigen (TMA) observed in exposed subjects relative to controls. General prevalence of detected autoantibodies higher in exposed subjects relative to controls.
Dose response presence/absence:	
Biases identified by the authors:	Immunologically susceptible workers may have left the plant or the area of exposure by the time of the study, potentially resulting in an underestimation of effect.
Assumptions/limitations of the study:	
Conclusions:	No persistent immnological effect was observed in exposed workers.
Reviewer Comments	

Information for Dose-Response Assessment	Although the mean duration of exposure was 7.9 years, the actual exposures to Hg had ceased on average 12.3 years before the study (range 1.0-35.0). The potential for effects to have reversed during this period should be considered. The HgU results also may not be accurate assessments of exposure, given that the half-life for HgU excretion is about 40-days and HgB half-live is about 3-days. Therefore this study is not included in the dose-response assessment.

Epidemiological Study Critical Evaluation Form

Reference:	Ellingsen, D.G., Bast-Pettersen, R., Efskind, J., and Y. Thomassen. 2001. Neuropsychological effects of low mercury vapor exposure in chloralkali workers. Neurotoxicology. 22: 249-258.
Toxicological Endpoint:	Neurological

Criteria	
Peer reviewed:	Yes
Type of study:	Cross-sectional
Population(s) studied:	Occupational: chloralkali workers
Case identification/definition	
Sample size:	47
Stratification (age, sex, etc.):	None
Control identification/definition	
Sample size:	47
Matching Criteria:	Age
Group selection method:	Men with exposure to mercury vapor for at least 1 year in a contaminated area of a plant under study were eligible for inclusion in the exposure group. Control group included men employed by the same company at the same industrial complex and had no known current or past occupational exposure to mercury. Exclusion criteria included alcohol abuse, major head injuries, metabolic disorders and major psychiatric, neurological or other diseases causing severe disability.
Data source for group information:	Medical examination, and interview emphasizing occupational and medical history, sociodemographic background and alcohol consumption.
Outcome(s) studied:	Subjective symptoms, general intellectual ability, visuomotor speed and attention, immediate memory/attention span, motor test and sustained visual attention and reaction time.
Exposure definition:	Average exposure of 42 (range of 24.0 - 66.8) and 41.9 years (range of 23.3 - 64.2) among exposure and control groups, respectively.
Exposure measurement:	HgU and HgB concentrations assessed, at the time of study and historical HgU concentrations obtained from routine measurements within the plant.
Duration of exposure applicable to measurement (i.e. acute, chronic):	Chronic. Average duration of exposure was 13.3 years.

Exposure levels:	Before study: Average HgU = 5.9 nmol/mmol Cr During study: HgB_{total} 43.5 nmol/l (range 10-108), HgB_{inorg}(nmol/l) 20.7 (range 2.5-65) Historical: Average HgU = 9.0 nmol/mmol Cr. Urine samples were collected at the plant since 1949.
Data adjustments:	Distributions of effect measure with skewness escedding 2.0 were log-transformed to achieve normalization. HgU levels detected before 1982 were adjusted for creatinine by the authors.
Results	
Relative Risk, Odd Ratio, Confidence Interval:	Not applicable
Statistics	
Procedures/tests:	Variance analysis: group comparisons Multiple linear regression analysis (backward procedure): association between neuropsychological test results and age, shift work, alcohol consumption, current smoking habits, history of head injury with concomitant unconsciousness and the raw score in the Information Test as potential confounders. Two-tailed P-values: reported throughout.
Statistically significant findings:	Positive association between number of symptoms and age, smoking and shift work was found. Exposure group had statistically significant better scores on the general intellectual ability test than the controls. A statistically significant association between the number of symptoms and age, smoking habits and shift work was observed.
Non-statistically significant findings:	Number of symptoms was not associated with any of the exposure measures. No significant differences between exposed and control subjects were observed for neuropsychological test performance (with the exception of general intellectual ability). However, slightly reduced performance in neuropsychological tests for visuomotor/psychomotor speed and attention, and immediate visual memory was observed in association with exposure. The clinical significance of these slight reductions is unknown.
Dose response presence/absence:	
Biases identified by the authors:	Age, smoking habits and shift history of the individuals may have influenced performance in some of the tests.
Assumptions/limitations of the study:	There is no explanation for the test performance being better among the exposure group. This is not attributed to differences in exposure.

Conclusions:	No significant differences were observed between exposed workers and control workers with respect to neuropsychological test results or subjective symptoms. When controlled for general intellectual ability, smoking, age and shift history, a statistical association between exposure and reduced performance in attention, psychomotor/visuomotor speed, and immediate visual memory were observed.
Reviewer comments	Although HgU monitored since 1949, cold vapour atomic absorption not used until the 1960's, and results were not adjusted for creatinine until 1982. HgU levels before 1982 were adjusted by the authors. Cumulative HgU exposure indices were calculated based on historical data. Timing of collection of urine samples not clear; and method and timing of collection for historical samples not clear.

Information for Dose-Response Assessment	No statistically significant association between Hg exposure and the incidence of neurological effects was observed. Only a weak association was observed after confounding factors were controlled for. This study is not included for consideration in the dose-response assessment as some effects are inconsistent with the general understanding of Hg toxicity, there is little association with HgB_{inorg} and effects and because the effects may be related mainly to current exposure to Hg, instead of chronic exposure.