Epidemiological Study Critical Evaluation Form

Reference:	Piikivi, L. and U. Tolonen. 1989. EEG findings in chlor-alkali workers subjected to low long term exposure to mercury vapour. Br. J. Ind. Med. 46: 370 - 375.
Toxicological Endpoint:	

Criteria	**Evaluation**
Peer reviewed:	Yes
Type of study:	Cross-sectional
Population(s) studied:	Occupational: chlor-alkali plant
Case identification/definition	
Sample size:	41
Stratification (age, sex, etc.):	None
Control identification/definition	
Sample size:	41
Matching Criteria:	Age and sex
Group selection method:	Exposed group were men in a chlorine-alkali plant who had been employed for at least five years. Individuals were excluded from the study if they had neurological, psychiatric and metabolic diseases, hypertension, skull injuries and a history of mercury intoxication. Exclusion criteria from the control group included earlier occupational exposure to heavy metals, wood conserving chemicals or solvents and a history of diseases or injuries used as exclusion criteria for the exposed group.
Data source for group information:	For the exposed group, information was obtained from bi-annual health examination records and case records.
Outcome(s) studied:	Visually interpreted electroencepthalography (EEG) and quatitative computerised EEG (cEEG).
Exposure definition:	Occupational exposure with exposure time varying between 5 and 27 years.
Exposure measurement:	Mercury concentration in urine (HgU) measured in samples collected the morning of the examination. Inorganic mercury in the blood (HgB), organic mercury in the blood (HgBorg) and total mercury in the blood (HgBtot). The time-weighted average (TWA) concentration of mercury in blood was determined based on data from 1969 until the beginning of the study.
Duration of exposure applicable to measurement (i.e. acute, chronic):	Exposed group have had chronic exposure and TWA of HgB (from 1969 to present) provides information on chronic exposure levels.
Exposure levels:	HgU of 11.6 (± 7.4) µmol/mol creatinine; HgB of 38.8 (± 24.5) nmol/L; HgBorg of 19.1 (± 10.8) and HgBtot of 58 (± 26.5). TWA HgB of 34.9 nmol/L; TWA HgBtot of 59 nmol/L.

Data adjustments:	For some analyses, the data for workers who work the day shift and the three-shift were seperated.
Results	
Relative Risk, Odd Ratio, Confidence Interval:	Not relevant
Statistics	
Procedures/tests:	Student's t-test
Statistically significant findings:	Exposure levels of day workers was significantly larger than the three-shift workers. cEEG parameters of mean frequency, delta, theta, alpha and beta frequency, total power and RMS were all significantly lower in the exposed group as compared to the control group. When comparison of the dayworker and the control group were made only the alpha frequency was statistically different. When comparison of the three-shift worker and the control group were made all the cEED parameters were significantly different.
Non-statistically significant findings:	The visually interpreted EEG showed a greater occurrence of EEG abnormalities, however, the differences were not statistically significant.
Dose response presence/absence:	No suggestion of a dose effect relation was found.
Biases identified by the authors:	The shift work was a confounding factor. Possible influence of exposure to organic mercury on the cEEG could not be controlled in the study.
Assumptions/limitations of the study:	
Conclusions:	It was concluded that the slowing and attenuation of the cEEG was related to exposure to Hg vapour. The strain caused by shiftwork accentuated the disturbance of the EEGs. A longitudinal study design wouild be needed to verify the suggestive results.
Reviewer Comments	The results are considered suggestive, and the authors indicate they need to be verified. Based on the air to blood ratio provided by Roels et al. 1987, the authors provided an mercury concentration in air of 25 µg/m3. This value is based on the total mercury in air. Given that our assessment is focused on elemental mercury, an air concentration of 15.6 µg/m3 was calculated based on the TWA of inorganic mercury in blood of 34.9 nmol/L (or 0.70 ug/dL).

Information for Dose-Response Assessment	This study is not recommended for the dose-response assessment as the authors have indicated that the results need to be verified.

Epidemiological Study Critical Evaluation Form

Reference:	Piikivi, L. and H. Hanninen. 1989. Subjective symptoms and psychological performance of chlorine-alkali workers. Scand. J. Work Environ. Health. 15: 69 - 74.
Toxicological Endpoint:	Neurological

Criteria	**Evaluation**
Peer reviewed:	Yes
Type of study:	Cross-sectional
Population(s) studied:	Occupational: chlorine-alkali workers
Case identification/definition	
Sample size:	60 (male)
Stratification (age, sex, etc.):	None
Control identification/definition	
Sample size:	60 (male) from a wood processing plant.
Matching Criteria:	Age, sex, vocational status and length of education.
Group selection method:	Exposed group were men in a chlorine-alkali plant who had been employed for at least five years. Individuals were excluded from the study if they had neurological, psychiatric and metabolic diseases, abuse of alcohol, skull injuries and hypertension. Participants were excluded from the control group if they had been exposed to neurotoxic chemicals or had a history of he same diseases and injuries listed as exclusion criteria for the exposed group. The day of the examination, each subject was interviewed about medical and occupational history, present health status and lifestyle.
Data source for group information:	For the exposed group, information was obtained from bi-annual health examination records and case records. For the control group, information was obtained from medical records. The judgement of the occupational health staff was also taken into consideration.
Outcome(s) studied:	Subjective symptoms and psychological performance (i.e psychomotor tests and memory and learning tests).
Exposure definition:	Occupational exposure
Exposure measurement:	Mercury concentration in urine (HgU) measured in samples collected in the morning of the examination. Inorganic mercury in the blood (HgB), organic mercury in the blood (HgBorg) and total mercury in the blood (HgBtot). The time-weighted average (TWA) concentration of mercury in blood was determined based on data from 1969 until the beginning of the study.

Duration of exposure applicable to measurement (i.e. acute, chronic):	Exposed group have had chronic exposure and TWA of HgB provides information on chronic exposure levels.
Exposure levels:	HgU of 10.1 (±6.8) µmol/mol creatinine; HgB of 33.8 (±22.7) nmol/L; HgBorg of 18.1 (±9.9) nmol/L and HgBtot of 51.9 (±25) nmol/L. TWA HgB of 29.6 nmol/L; TWA HgBtot of 51.3 nmol/L.
Data adjustments:	For some analyses, the data for workers who work the day shift and the three-shift were seperated.
Results	
Relative Risk, Odd Ratio, Confidence Interval:	Not relevant.
Statistics	
Procedures/tests:	Paired t-tests
Statistically significant findings:	The exposed day workers had significantly higher HgB and HgU than the three-shift workers. In the psychological tests, the only test where the results were significantly different between the exposed and control groups was in the continuous performance test. However, the performance was better among the exposed group in comparison to the controls. In the test for subjective symptoms a comparison of scores between controls and three-shift workers identified statistically significant differences in memory disturbances, sleep disorders, fatigue and confusion. A comparison of scores between controls and day workers identified statistically significant differences in memory disturbances and tremor of hands. A two-way analysis of variance indicates that memory disorders were significantly associated with the form of workshift but not with the level of exposure.
Non-statistically significant findings:	In the psychological tests, there was no significant difference between the exposed and the control groups for the finger tapping, continuous performace, symbol digit substitution and pattern comparison tests. There were no significant differences between the exposed and the control groups for the memory and learning tests (i.e. associate learning, associate recall, pattern memory test and serial digit learning).
Dose response presence/absence:	Not addressed.
Biases identified by the authors:	Strain in the three-shift work was a possible cofactor for subjective disturbances such as sleep disorders, fatigue and confusion.
Assumptions/limitations of the study:	

Conclusions:	It was concluded that no significant adverse effects were identified in relation to long-term exposure to mercury at a concentration of 25 $\mu g/m^3$.
Reviewer Comments	

Information for Dose-Response Assessment

This study is recommended for inclusion in the dose response assessment. Based on the air to blood ratio provided by Roels et al. 1987, the authors provided an mercury concentration in air of 25 $\mu g/m^3$. It appears that this value is based on the total mercury in air. Given that our assessment is focused on elemental mercury, an air concentration of 13.2 $\mu g/m^3$ was calculated based on the TWA of inorganic mercury in blood of 29.6 nmol/L (or 0.59 ug/dL). This is considered a NOAEL.

Epidemiological Study Critical Evaluation Form

Reference:	Liang, Y.-X., Sun, R.-K., Sun, Y., Chen, Z.-Q., and L.-H. Li. 1993. Psychological effects of low exposure to mercury vapour: Application of a computer-administered neurobehavioural evalutaion system. *Environ. Res.* **60**: 320 - 327.
Toxicological Endpoint:	Neurological

Criteria	**Evaluation**
Peer reviewed:	Yes
Type of study:	Cross-sectional
Population(s) studied:	Occupational: fluorescent lamp factory
Case identification/definition	
Sample size:	88 (19 male and 69 female)
Stratification (age, sex, etc.):	None
Control identification/definition	
Sample size:	70 (46 male and 24 female)
Matching Criteria:	None
Group selection method:	Study group were employees at a fluorescent lamp factory. They had uninterrupted occupational exposure to Hg vapour for at least 2 years prior to the study. Average years of exposure is 10.4 years. It is not identified where the members of the control group were obtained. In both groups no neurological or neuropsychiatric disorders were identified in the medial history of the participants.
Data source for group information:	Not identified.
Outcome(s) studied:	Profile of mood states (POMS) and a computerized neurobehavioural test consisting of 20 subtests adapted for testing intelligence, memory, visual perception and psychomotor functions.
Exposure definition:	Occupational exposure as a result of working in a fluorescent lamp factory.
Exposure measurement:	Mercury concentrations in urine (HgU) were measured from 24-hr urine samples. Mercury concentrations in air were measured in fixed locations for 4 - 8 hrs.
Duration of exposure applicable to measurement (i.e. acute, chronic):	The workers participating in this study have had chronic exposure.
Exposure levels:	Mercury vapour in the air had an average concentration of 33 $\mu g/m^3$ (range of 8 to 85 $\mu g/m^3$). Urinary excretion of 25 ± 59 µg/L.

Data adjustments:	Data adjustments for chronological age were made when assessing neurobehavioural effects. Note: there were no significant differences in smoking, alcohol consumption, computer experience, years of school and years of working between the exposed and control groups.
Results	
Relative Risk, Odd Ratio, Confidence Interval:	Not relevant.
Statistics	
Procedures/tests:	
Statistically significant findings:	Two of the mood states in the POMS (fatigue and confusion) were significantly higher in the exposed group compared to controls. In the statistical analysis of the results for the neurobehavioural tests, analysis of covariance was conducted to exclude the confounding effect of chronological age. After controlling for chronological age, statistically significant differences between the exposed and control groups in mental arithmetic ($P<0.05$), paired-associate learning ($P<0.05$), two-digit search ($P<0.01$), switching attention and reaction time ($P<0.05$) and pattern comparison ($P<0.05$) were identified.
Non-statistically significant findings:	Overall score for POMS was not significantly different between exposed and control groups. Statistically significant differences were not observed among the following neurobehavioural tests: visual retention, paired-associate learning, symbol digit substitution, minimum time consumed in two-digit search, mean reation time in the visual SRT, mean visual CRT and pattern comparison.
Dose response presence/absence:	Not addressed.
Biases identified by the authors:	None
Assumptions/limitations of the study:	HgU was not corrected for creatinine.
Conclusions:	Exposure to low levels of Hg leads to increased in negative mood states and an alteration of neuorbehavioural patterns which are likely connected to cognitive function impairment. After biological age was controlled for, subjects with longer working exposure (in years) exerted a poorer neurobehavioural performance. This may imply cumlative effects on psychological function.

Reviewer Comments	Information concerning exposure measurements is limited. The number of days in which air samples and the number of urine samples collected is not provided. It appears that air samples were only collected on one day. Area, rather than personal, air samples were used to characterize airborne exposure levels. There was no examination to determine if HgU or Hg in air correlates with test scores.

Information for Dose-Response Assessment	Within this study there was no analysis to relate the observed effects with Hg exposure. As such the observed effects may have been related to other occupational exposures. In addition the quality of the exposure information is considered poor (i.e HgU concentrations were not adjusted for creatinine and air concentration measured by an area sampler and only over one day). As such, this study is not recommended for inclusion within the dose-response assessment.

Epidemiological Study Critical Evaluation Form

Reference:	Fawer, R.F., DeRibaupierre, U., Guillemin, M.P., Berode, M., and M. Lobe. 1983. Measurement of hand tremor induced by industrial exposure to metallic mercury. Br. J. Ind. Med. 40: 204 - 208.
Toxicological Endpoint:	

Criteria	**Evaluation**
Peer reviewed:	Yes
Type of study:	Cross-sectional
Population(s) studied:	Occupational
Case identification/definition	
Sample size:	26 (male): 7 form a fluorescent tube factory, 12 from a chloralkali plant and 7 from a chemical plant.
Stratification (age, sex, etc.):	None
Control identification/definition	
Sample size:	25 (male)
Matching Criteria:	None
Group selection method:	Control group members were from the same factories as the exposed group but were never occupationally exposed. Method for selecting exposed group was not discussed.
Data source for group information:	Not addressed.
Outcome(s) studied:	Hand tremor measurements.
Exposure definition:	Occupational exposure of workers in factories that involve the use of mercury. Average exposure of 15.3 years (range of 1 to 41 years).
Exposure measurement:	Mercury concentration in urine (HgU) from night samples. Mercury concentrations in blood (HgB). Mercury concentrations in air, collected with personal air samplers.
Duration of exposure applicable to measurement (i.e. acute, chronic):	Chronic
Exposure levels:	In the exposed group the average concentration of mercury in blood (HgB) and in urine (HgU) were 41.3 µmol/L and 11.3 µmol/mol creatinine (20 µg/g creatinine), respectively. The time-weighted average (TWA) for personal exposure was 26 $\mu g/m^3$.
Data adjustments:	
Results	
Relative Risk, Odd Ratio, Confidence Interval:	Not relevant.
Statistics	

Procedures/tests:	Student t tests between crude indices of tremor of exposed and control groups. Multiple regressions including duration of exposure, age and concentration of HgU or HgB were fitted, choosing the one that gave the smallest residual mean square.
Statistically significant findings:	Mean Highest Peak Frequencies (HPFs) at rest were higher in the exposed group than the controls. Based on an analysis of variance, age and duration of exposure are the most relevant predictor variables. The exposed and control group both showed significant decreases in the HPF between rest and load. A test of difference was significant between the exposed and control group. Again, age and duration of exposure were the most relevant predictor variables. The mean change betwen rest and load was significant among the exposed group (but not the controls). When looking at the change in control and exposed men the mean residual squares were the least with only duration and $\log_e$ HgU as predictor variables.
Non-statistically significant findings:	The second moment (M2) was not significantly different among the control and exposed groups. The change in M2 between rest and load was not statistically significant among the control group.
Dose response presence/absence:	Not addressed.
Biases identified by the authors:	None identified.
Assumptions/limitations of the study:	Histories of exposure for each of the exposed workers is not well known.
Conclusions:	Highest peak frequences were higher in exposed men than in the controls and were related to duration of exposure and to age. However, age was negatively related to HPF. The most important predictor variable of hand tremor was always the duration of exposure.
Reviewer Comments	Very little information is provided regarding the air sampling, the collection of urine and blood samples or how the study participants were selected. No information is provided on other simultaneous exposures that may occur in their work environments. Within this study the best predictor was duration of exposure, it is difficult to conclude that the effects are from mercury and not some other substance/condition that is related to the work condition. However, Loge HgU was identified as a predictor variable for the change in M2.

Information for Dose-Response Assessment	This study is recommended for inclusion in the dose-response assessment. The average level of exposure was 26 $\mu g/m^3$. This is considered a LOAEL.

Epidemiological Study Critical Evaluation Form

Reference:	Piikivi, L. 1989. Cardiovascular reflexes and low long-term exposure to mercury vapour. Int. Arch. Occup. Environ. Health. 61: 391 - 395.
Toxicological Endpoint:	

Criteria	**Evaluation**
Peer reviewed:	Yes
Type of study:	Cross-sectional
Population(s) studied:	Occupational: chlor-alkali plant
Case identification/definition	
Sample size:	41
Stratification (age, sex, etc.):	None
Control identification/definition	
Sample size:	41
Matching Criteria:	Age and sex.
Group selection method:	Exposed group were men in a chlorine-alkali plant who had been employed for at least five years. Individuals were excluded from the study if they had neurological, psychiatric and metabolic diseases, alcohol abuse, hypertension, skull injuries or a history of mercury intoxication. The control group were from a wood processing plant. Exclusion criteria from the control group included earlier occupational exposure to heavy metals, wood conserving chemicals or solvents and a history of diseases or injuries used as exclusion criteria for the exposed group.
Data source for group information:	For the exposed group, information was obtained from bi-annual health examination records and case records. For the control group, information was obtained from medical records. The judgement of the occupational health staff was also taken into consideration.
Outcome(s) studied:	Subjective symptoms related to autonomic dysfunction and cardiovascular reflex response (pulse rate variations and blood pressure reactions).
Exposure definition:	Occupational exposure with exposure time varying between 5 and 27 years.
Exposure measurement:	Mercury concentration in urine (HgU) measured in samples collected the morning of the examination. Inorganic mercury in the blood (HgB), organic mercury in the blood (HgBorg) and total mercury in the blood (HgBtot). The time-weighted average (TWA) concentration of mercury in blood was determined based on data from 1969 until the beginning of the study.

Duration of exposure applicable to measurement (i.e. acute, chronic):	Exposed group have had chronic exposure and TWA of HgB (from 1969 to present) provides information on chronic exposure levels.
Exposure levels:	HgU of 96.6 nmol/L (11.6 ± 7.4 μmol/mol creatinine); HgB of 38.8 (± 24.5) nmol/L; HgBorg of 19.1 (± 10.8) nmol/L and HgBtot of 58 (± 26.5) nmol/L. TWA HgB of 34.9 nmol/L; TWA HgBtot of 59 nmol/L.
Data adjustments:	
Results	
Relative Risk, Odd Ratio, Confidence Interval:	Not relevant.
Statistics	
Procedures/tests:	
Statistically significant findings:	The only subjective symptom that was statistically different in the exposed group in comparison to the control group was the occurrence of palpitations. The only cardiovascular reflex response that was significantly different in the exposed group when compared to the control group was the diastolic blood pressure at 1 minute (not at 2, 3 or 4 minutes). The HgU and beat-to-beat variation of the heart rate had a statistically significant positive correlation.
Non-statistically significant findings:	No statistically significant differences in vertigo, orthostatic dizziness, perspiration, diarrhoea, frequent urination or impotence between the exposed and control groups. No statistically significant differences in the pulse rate variation and blood pressure reactions between the exposed and control groups. The rise of the diastolic BP of the exposed group was not
Dose response presence/absence:	Not addressed.
Biases identified by the authors:	Not addressed.
Assumptions/limitations of the study:	
Conclusions:	A tendency for smaller pulse rate variations and for more palpitations (subjective) was identified among exposed workers.

Reviewer Comments	Professional judgement of occupational staff was used in the selection of referents. No details were provided on what this involved. This process could bias the results. The study did not exclude migraine sufferers (1 exposed and 1 referent). There is no information provided within this study to indicate that the observed effects are due to impacts on the neurological system as opposed to effects on the cardiovascular system.

Information for Dose-Response Assessment	The observed effects may be due to impacts on the cardiovascular system, as opposed to neurological system, and therefore this study is not included in the dose-response assessment.

Epidemiological Study Critical Evaluation Form

Reference:	Ngim, C.H., Foo, S.C., Boey, K.W., and J. Jeyaratnam. 1992. Chronic neurobehavioral effects of elemental mercury in dentists. Br. J. Ind. Med. 49: 782 - 790.
Toxicological Endpoint:	Neurobehavioural

Criteria	**Evaluation**
Peer reviewed:	Yes
Type of study:	Cross sectional
Population(s) studied:	Occupational: Dentists in Singapore
Case identification/definition	
Sample size:	98 (38 women and 60 men)
Stratification (age, sex, etc.):	None
Control identification/definition	
Sample size:	54 (27 women and 27 men)
Matching Criteria:	None.
Group selection method:	Control group were selected from staff at the national University of Singapore and had no history of occupational exposure to mercury.
Data source for group information:	Questionnaires used for dentists and controls. Participants had no history of neuropathy from diabetes, renal diseases and escessive alcohol use, disease of the central or peripheral nervous system or psychiatric disorders, surgery or injuries to arms or legs, or head or spinal cord surgery or injuries.
Outcome(s) studied:	Neurobehavioural evaluation: visual reproduction, bender gestalt, logical memory, block design, seashore rhythm and profile of mood tests. Intelligence tests: block design test, similarity, comprehension and picture completion. These are four subtests of the Wechsler adult intelligence scale revised.
Exposure definition:	Dentist exposed during work hours.
Exposure measurement:	Mercury concentration in blood (HgB) and in the air.
Duration of exposure applicable to measurement (i.e. acute, chronic):	Exposure to dentists has been chronic. However, measurements only relate to acute exposure (i.e. air concentrations over a day or week and a blood sample).
Exposure levels:	Exposure measured among the dentists with diffusive personal sampling badges over a working day (8 to 10 hours). Exposure to an average personal air Hg concentration of 0.014 mg/m^3 (0.0007-0.042 mg/m^3). Exposure occurred for a mean of 5.5 years (range of 0.7 - 24). Mercury in blood measured towards the end of the work day. Four dentists were monitored through a work week to assess daily variation.

Data adjustments:	For analysis the dentists were categorised into four exposure subgroups. A statistically significant difference between the years of education and the used of traditional Chinese medicinal products that might contain mercury. In addition, the sex distribution was not identical. These factors were adjusted for in the statistical analysis. Note: the groups were well matched in age, amount of fish consumed and number of amalgam fillings. The product of the the exposure intensity (TWA) and the duration of exposure (months) was used as a surrogate for dose.
Results	
Relative Risk, Odd Ratio, Confidence Interval:	Not relevant.
Statistics	
Procedures/tests:	Analyses of covariance used to test difference between exposed group and control group. Regression analysis with the general linear models procedure used to determine dose-effect relationship between neurobehavioural performance and exposure. PROC and GLM procedure used for analysis of covariance and regression analysis.
Statistically significant findings:	Exposed group was significantly better in the comprehension test compared to the control group. Statistically significant difference between the exposed and control groups for neurobehavioural effects were identified in the finger tapping, trail making, symbol digit, digit span, logical memory recall, visual reproduction (immediate and delayed recall) and Bender gestalt time scores tests. Dose-effect between performance scores and dose was statistically significant for finger tapping, trail making, symbol digit, digit span, logical memory delayed recall, visual reproduction (immediate and delayed recall) and block design time tests. Note that the dose surrogate was used for this calculation. The dentists were split into high and low groups for exposure and duration. Higher exposed subgroups had statistically significant poorer performance in the digit sypmbol, digit span, trail making, logical memory delayed recall and visual reproduction delayed recall tests that the low exposure group. A significant increase in aggressive mood was identified among the exposed group in comparison to the control group.
Non-statistically significant findings:	No significant differences were detected in the similarity, picture completion and block design scores between the exposed and control group. The average standard score for the four intelligence tests was not significantly different between the exposed and control groups.

Dose response presence/absence:	Dose effect identified for some neurobehavioural tests.
Biases identified by the authors:	Dentists are exposed to vibration and physical load at the hands, wrists and arms when using drilling and grinding tools. This may affect motor speed (finger tapping speed) and manual dexterity (grooved peg board time). Older dentists may have worked under different conditions (e.g. air conditioning) than the younger dentists, leading to differences in exposure levels.
Assumptions/limitations of the study:	
Conclusions:	Performance of dentists in most of the neurobehavioural tests was significantly worse than the controls and a dose effect was seen between cumulative dose and performance. Results may indicate signs of early damage to the central and peripheral nerves.
Reviewer Comments	Information concerning exposure to mercury is limited. The concentration of mercury in air was measured for only one day for the majority of the participants and this single measurement formed the basis of the dose estimate. For four dentists, mercury concentrations in air were measured for a week. An increase in aggression with dose could be a function of the duration of time in the occupational, rather than Hg exposure. In this study the product of the the exposure intensity (TWA) and the duration of exposure (months) was used as a surrogate for dose. If is difficult to determine if the statistically significant effects are a result of duration, mercury exposure or both. The authors attempt to address this, however, their analysis is limited.

Information for Dose-Response Assessment	Although, this study contains some limitations, it is recommended for inclusion in the dose-response assessment. The authors calculated an average TWA of 14 μg/m^3. This is considered a LOAEL.