Epidemiological Study Critical Evaluation Form

Reference:	Sandborgh-Englund, G., Nygren, A.T., Ekstrand, J., and C.G. Elinder. 1996. No evidence of renal toxicity from amalgam fillings. Amer. J. Physiol. 271(4):R941 – R945.
Toxicological Endpoint:	Renal function

Criteria	
Peer reviewed:	Unknown. Enquiry has been sent to publisher.
Type of study:	
Population(s) studied:	Dentistry patients
Case identification/definition	
Sample size:	10 (7 male, 3 female)
Stratification (age, sex, etc.):	None
Control identification/definition	
Sample size:	None
Matching Criteria:	Not applicable.
Group selection method:	Healthy volunteers that agreed to have all amalgam fillings removed on one occasion and replace them with cast inlays, crowns or composite fillings.
Data source for group information:	Medical examination
Outcome(s) studied:	Glomerular filtration rate (GFR) and effects on the excretion of NAG, β_2-microglobulin, albumin, creatinine
Exposure definition:	Exposure during removal of fillings.
Exposure measurement:	Mercury concentrations in urine (HgU) and blood (HgB).
Duration of exposure applicable to measurement (i.e. acute, chronic):	acute and chronic
Exposure levels:	
Data adjustments:	Some parameters were transformed to normality by logarithmic transformation.
Results	
Relative Risk, Odd Ratio, Confidence Interval:	Not relevant.
Statistics	
Procedures/tests:	Analysis of variance, repeated measures design: changes in any of the measure parameters Contrast analysis: comparisons between days

Statistically significant findings:	Significantly increased plasma Hg was observed immediately following amalgam removal, but decreased to half the pre-treatment values 2-months post-removal.
Non-statistically significant findings:	No significant changes in urinary excretion of albumin, β_2-microglobulin, or NAG were observed, and the relative clearance of β_2-microglobulin was unchanged. No significant correlation between HgB (blood and plasma) or HgU and renal endpoints were observed.
Dose response presence/absence:	No correlation between HgB or HgU and renal effects
Biases identified by the authors:	
Assumptions/limitations of the study:	Subjects not occupationally exposed to Hg or had amalgam treatment within the last year. Also assumes that all subjects did not consume fish as directed.
Conclusions:	No signs of renal toxicity were observed in association with exposure to amalgam fillings
Reviewer Comments	24-hour urine samples collected. Blood and urine samples collected 1-week prior to amalgam removal and 1, 2, and 60-days after. Authors note that the assessment of Hg pharmacokinetics is difficult due to a lack of precision in analysis at low-exposure levels and potential contributions from other sources of Hg.

Information for Dose-Response Assessment	Rather than occupational exposures, this study examined individuals before and after the removal of amalgam fillings. Although the average number of fillings was known, the actual levels of Hg vapour to which the individuals were exposed is unknown and may have been variable. Also, various factors may affect the release of Hg from amalgam. The duration of exposure to Hg was also not well known. This study does not contain enough information to characterise Hg exposure to be of use in the dose response assessment.

Epidemiological Study Critical Evaluation Form

Reference:	Stromberg, R., Langworth, S., and E. Soderman. 1999. Mercury inductions in persons with subjective symptoms alleged to dental amalgam fillings. Eur J Oral Sci 107: 208 - 214.
Toxicological Endpoint:	

Criteria	
Peer reviewed:	Unknown. Enquiry sent to publisher.
Type of study:	Double-blind study
Population(s) studied:	Volunteers who suspected themselves as having "amalgam disease".
Case identification/definition	
Sample size:	39 (16 male, 23 female)
Stratification (age, sex, etc.):	None
Control identification/definition	
Sample size:	Not relevant
Matching Criteria:	Not relevant
Group selection method:	Volunteers responding to advertisements in two local papers in the County of Skaraborg, Sweden.
Data source for group information:	Medical examination and self-assessment of reaction to Hg.
Outcome(s) studied:	General appraisal of reaction during a 7 day period following the treatment. Registration of the intensity of all their different symptoms using a five-point graded scale, each day.
Exposure definition:	
Exposure measurement:	
Duration of exposure applicable to measurement (i.e. acute, chronic):	Acute
Exposure levels:	Subjects were exposed to Hg at levels of 0, 25, 50, 100 or 200 µg, in successive doses of 5-10 minute duration, administered in random sequence (unknown to subject and operator).
Data adjustments:	
Results	
Relative Risk, Odd Ratio, Confidence Interval:	Not relevant
Statistics	
Procedures/tests:	One-sided Fisher's exact test Student's t-test (two-sided)

Statistically significant findings:	Significantly increased mean intensity of uro-genital symptoms was observed when intensity scores examined on an individual basis.
Non-statistically significant findings:	No statistically significant increase in the frequency of reactions following Hg exposure when compared with pure air exposure. No significant difference in the mean intensity of all symptoms was observed. No significant evidence of sensitivity to Hg exposure was observed based on results between exposed and non-exposed periods.
Dose response presence/absence:	Not calculated, however increased reactions were not identified in relation to increased Hg dose.
Biases identified by the authors:	Subjects selected their own endpoints of effect or reaction - not clearly defined and were therefore inconsistent. Appriasal of intensity of reactions was also variable and not well defined. Results from subjects who dropped out due to illness were not included in the results; the authors identify that the illnesses/effects should have been included as potential effects of relevance.
Assumptions/limitations of the study:	Although one subject had occupational Hg exposure, and two other were exposed to methylmercury from fish, it was assumed that this was not associated with any effects.
Conclusions:	Short-term exposure to low-doses of Hg was not associated with the promotion of clinical illness.

Information for Dose-Response Assessment	This study involved exposure to small yet controlled doses (0.6 - 10 μg) Hg vapour. However, the effect of endpoints were subjective and not well defined. Biological monitoring was not conducted. This study does not contain information regarding defined, physiological endpoints of effect and therefore should not be included in the dose-response assessment.

Epidemiological Study Critical Evaluation Form

Reference:	Urban, P., Gobba, F., Nerudova, J., Lukas, E., Cabelkova, Z., and M. Cikrt. 2003. Color discrimination impairment in workers exposed to mercury vapor. Neurotoxicology 24: 711-716.
Toxicological Endpoint:	Neurological

Criteria	
Peer reviewed:	Yes
Type of study:	Cross sectional
Population(s) studied:	Occupational:chloralkali plant workers
Case identification/definition	
Sample size:	24
Stratification (age, sex, etc.):	None (all male, mean age of 42 years)
Control identification/definition	
Sample size:	24
Matching Criteria:	Age and gender
Group selection method:	Not identified.
Data source for group information:	Not identified.
Outcome(s) studied:	Color discrimination impairment: Lanthony test (15-Hue desaturated test for colour vision); Bowmans Color Confusion Index (CCI); qualitative assessment with Verriest's classification of acquired dyschromatopsias.
Exposure definition:	Occupational exposure in a chloralkali plant.
Exposure measurement:	Mercury concentrations in urine (HgU) and in air.
Duration of exposure applicable to measurement (i.e. acute, chronic):	Chronic
Exposure levels:	Level of Hg in plant (TWA) determined to be 59 μg/$m^{3.}$ Mean HgU in workers determined to be 20.5 μg/g creatinine (range 0.15 - 61.7 μg/g creatinine).
Data adjustments:	Exposed and control groups compared with respect to age, alcohol intake, and smoking.
Results	
Relative Risk, Odd Ratio, Confidence Interval:	Not applicable
Statistics	
Procedures/tests:	Non-parametric Mann-Whitney U-test: intergroup comparisons Chi-squared test: compare frequencies Multiple regression analysis: association between the color confusion index and various independent variables.

Statistically significant findings:	Statistically significant differences in color discrimination between the exposure and control group: scores on Colour Confusion Index were higher, frequency of subjects of errorless performance was decreased (all relative to controls).
Non-statistically significant findings:	Non-significant increase observed in the frequency of workers with Type II blue-yellow discrimination disorder.
Dose response presence/absence:	Not observed
Biases identified by the authors:	Alcohol and smoking significantly affected the proportion of workers with errorless performance.
Assumptions/limitations of the study:	Exposure to other agents in plant and their influence on the results not discussed.
Conclusions:	Hg vapour is associated with sub-clinical colour vision impairment in chronically exposed workers.
Reviewer Comments	Authors note that potential threshold for effect of Hg on colour perception may correspond to HgU levels between 10-20 μg/g. This range, and the HgU level in this study, all correspond with Hg exposures below current occupational hygiene recommendations.

Information for Dose-Response Assessment	This study was excluded from the dose-response assessment based on a number of factors. These include 1) there was no association between the effect and HgU; 2) limited information was provided on the group selection method and 3) limited information was provided on the air measurement and it appears that only one measurement was taken (i.e. only a single value was provided).

Animal Study Critical Evaluation Form

Reference:	Warfvinge, K., Hansson, H., and P. Hultman. 1994. Systemic autoimmunity due to mercury vapour exposure in genetically susceptible mice: Dose-responses studied. Toxicol. Appl. Pharm. 132: 299 – 309
Toxicological Endpoint	Immunological

Criteria	**Evaluation**
Peer review:	Yes
Type of study:	Bioassay
Animal(s)	
Species/Strain(s):	SJL/N (H-2^s) mice (female)
Body weight:	Not provided
Age:	7-8 weeks at beginning of the experiment
Sex:	Female
Control(s)	
Positive control:	None
Negative control:	One group left untreated to serve as a control.
Exposure Parameters	
Exposure concentrations:	Mice exposed to 0, 0.5, 0.5, 1.0, 0.3, 1.0, 0.5 mg/m^3 Hg. Resultant exposures were 75, 170, 360, 480, 690, or 2365 µg Hg/week/kg
Administration route:	Inhalation
Exposure schedule:	Mice exposed for 0.5 - 19-hours/day, 5 days a week for 10 weeks.
Exposure duration:	Different groups of mice exposed to 0.5, 1.5, 1.5, 6, 3 or 19 hours per day
Chamber design/type:	Stainless steel and glass walls of Rochester type.
Air changes/flow rate:	Air chamber, approximately 1m^3, was ventilated with an air flow of 2 m^3/hr.
Oxygen content/ temperature/relative humidity (in mean and variance):	Oxygen content: not provided; Temperature: 22°C; Humidity: 50%
Endpoints:	Antinuclear antibodies analysis, serum immunoglobulin concentrations, tissue immune deposits and mercury analyses.
Applicability of measurement endpoint to duration:	
Toxicological/biological relevance of exposure measurement:	
Results:	
Mortality	One mouse died in each the 75, 170 and 480 µg/week/kg group after 6, 8 and 8 weeks (respectively) within a few hours of blood sampling.
Clinical	Not described

Histopathological	In mice exposed to 170, 360, 480, 2365 µg Hg/week/kg, the dominant pattern of IgG antinucleolor antibody (ANoA) staining was distinct and clumpy. Similar patterns were not observed in pretreatment sera, controls, or the 75 µg Hg/week/kg group. Significant relationship between Hg dose and ANoA titre was observed. Mice in the 690 and 2365 µg Hg/week/kg groups demonstrated signifcantly increased serum IgG and IgE isotpyes (except at 10-weeks in the 2365 µg Hg/week/kg group). Mice in the 480 µg Hg/week/kg had significantly increased IgG1 and IgG2a levels after 2,4, and 6-weeks exposure. In the 360 µg Hg/week/kg group, Ig deposits were observed (not specified). A significant relationship between absorbed dose and individual titres of IgG, IgM and C3 was observed in the mesangium of mice.
Biochemical	All tissues analyzed from exposed mice demonstrated significantly increased Hg concentrations relative to controls. A significant correlation between calculated Hg dose and Hg levels in the various organs was observed. Increased Hg exposure was associated with increased Hg body burden (indicated by kidney Hg concentration).
Dose response presence/absence:	
Statistical analysis:	
Procedures/tests:	Student's t-test; Spearman's rank correlation
Biases identified by the authors:	
Assumptions/limitations of the study:	Diffferent species may vary in sensitivity to AnoA induction and immune-complex deposition in the kidneys/vessel walls.
Conclusions:	Hg vapour induced autoimmune syndrome (consistent with previous observations) in genetically susceptible mice, characterised by general stimulation of the immune system with hyperimmunoglobulinemia.
Reviewer Comments	H-2 mice are genetically susceptible to Hg, and are known to exhibit general activation of immune system with splenic cell hyperplasia, B-cell activation, increased number of immunolglobulin-secreting cells, and hyperimmunoglobulinemia. Authors note that the threshold for the induction of autoantibodies is estimated to be between 100 - 170 µg Hg/week/kg, and that the required dose for induction of AnoA in mice is similar between exposures to Hg vapour and $HgCl_2$ in drinking water.

Information for Dose-Response Assessment	A significant relationship between calculated absorbed Hg dose and renal Hg concentration levels. The absorbed doses were extrapolated from the actual air exposure levels in this study, and are clearly defined. The LOAEL for serum IgG antibucleolar antibodies (ANoA) of 170 μg Hg/week/kg was established (based on exposure to 0.5 mg/m3 for 1.5 hours/day). As such, the lower dose level of 75 μg Hg/week/kg (based on exposure to 0.5 mg/m3 for 0.5 hours/day) can be used as a NOAEL. This study should be included in the dose-response assessment.

Epidemiological Study Critical Evaluation Form

Reference:	White, R.F., Feldman, R.G., Moss, M.B., and S.P. Proctor. 1993. Magnetic resonance imaging (MRI), neurobehavioral testing, and toxic encephalopathy: Two cases. Environ. Res. 61:117-123.
Toxicological Endpoint:	Neurological

Criteria	
Peer reviewed:	Unknown
Type of study:	Case study
Population(s) studied:	Occupational: 48-year old hispanic male exposed at his job in a thermometer factory from 1981 to 1984.
Case identification/definition	
Sample size:	1
Stratification (age, sex, etc.):	Not relevant
Control identification/definition	
Sample size:	0
Matching Criteria:	Not relevant
Group selection method:	Evaluated in the Environmental and Occupational Neurology Program at Boston University Medical Center.
Data source for group information:	
Outcome(s) studied:	Neuropsychological testing and magnetic resonance imaging.
Exposure definition:	
Exposure measurement:	Mercury concentrations in urine (HgU).
Duration of exposure applicable to measurement (i.e. acute, chronic):	Chronic exposure that occurred historically.
Exposure levels:	HgU of 690 µg/L in August before chelation treatment. HgU level was 17 µg/L after chelation treatments.
Data adjustments:	
Results	
Relative Risk, Odd Ratio, Confidence Interval:	Not relevant
Statistics	No statistical analysis conducted.

Findings:	MRI results consistent with diffuse and focal white matter disease. Problems with cognitive flexibility, cognitive tracking, inhibiting perseveration, fine manual motor coordination, visuospatial analysis and organization, memory for visuospatial information, affect and personality. Free speech was within normal limits.
Dose response presence/absence:	Not addressed.
Biases identified by the authors:	Not addressed.
Assumptions/limitations of the study:	Study design, number of subjects and number of endpoints assessed.
Conclusions:	the study illustrated the value of neuropsychological measures in studying toxic encephalopathy.
Reviewer Comments	Purpose of study was more to assess the use of neuropsychological measures in toxic encephalopathy to quantify deficits and conform localized pathology in the subcortical regions of the brain, rather than the effects associated with exposure.

Information for Dose-Response Assessment	This study is not included in the dose response assessment given the design of this study (i.e. it only addressed one subject) and the historical nature of the exposure.

Epidemiological Study Critical Evaluation Form

Reference:	Yang, Y.J., Huang, C.C., Shih, T.H., and S.S. Yang. 1994. Chronic elemental mercury intoxication: Clinical and field studies in lampsocket manufacturers. Occup. Environ. Med. 51: 267-270.
Toxicological Endpoint:	Neurological

Criteria	
Peer reviewed:	Yes
Type of study:	
Population(s) studied:	Occupational exposure in a lampsocket manufacturing factory
Case identification/definition	
Sample size:	4 (3 male, 1 female)
Stratification (age, sex, etc.):	None
Control identification/definition	
Sample size:	0
Matching Criteria:	None
Group selection method:	Patient #1 identified as having high levels of mercury and lead in blood and urine after seeking medical attention. Exposure suspected from his work environment, a lampsocket manufacturing factory. The remaining workers at the factory, identified as patients 2, 3 and 4, were included in the study.
Data source for group information:	Interview and completion of a questionnaire.
Outcome(s) studied:	Clinical symptoms: gum pain, dizziness, fatigue, memory impairment, bad temper, irritabliity, back pain, nightmare, insomnia, body weight loss, excessive salivation, hyperhidrosis, blurred vision, tremor, writing difficulty, slurred speech, mental response, unsteady gait and distal limb numbness. Physical and neurological assessment: visual field defects, gingivitis, dysarthria, tremor, finger to nose test, heel to knee and shin test, gait disturbance, muscle strength and tendon reflexes. Modified minimental test.
Exposure definition:	Occupational exposure. Duration of exposure was from 1.5 to 7 years.
Exposure measurement:	Mercury concentrations in urine (HgU) and blood (HgB). Mercury concentrations in waste lampstems and air samples.
Duration of exposure applicable to measurement (i.e. acute, chronic):	Chronic

Exposure levels:	TWA in two work areas was sampled. In one working area the TWA was 0.709 mg/m^3 for worker 2 and 0.945 mg/m^3 for worker 1. In a seperate room the TWA was 0.225 mg/m^3. Before treatment/removal, HgB levels ranged from 237 and 105 µg/L in workers 1 and 2 respectively. 24-hour HgU concentrations ranged were 610 and 408 µg/L in workers 1 and 2, and spot urine tests in workers 3 and 4 were determined to be 110 µg/L and 90 µg/L.
Data adjustments:	
Results	
Relative Risk, Odd Ratio, Confidence Interval:	
Statistics	
Procedures/tests:	
Statistically significant findings:	Although no statistical analysis were conducted, the clinical progression of Hg intoxication was examined in this study. Early exposure appeared to be assocated with fatiue, memory impaiment, hypersalivation and hyperhidrosis. Within months, additional symptoms such as gum pain, poor attention, irritability and various psychiatric symptoms, unsteady gait, tremor, blurred vision, dysarthia and distal numbness may occur. Treatment by removing potential of exposure and/or low doses of D-penicillamine (150 - 300 mg/day).
Non-statistically significant findings:	
Dose response presence/absence:	Not applicable
Biases identified by the authors:	Not applicable
Assumptions/limitations of the study:	Not provided
Conclusions:	Complete recovery from chromic Hg intoxication may occur when the potential for exposure is removed.
Reviewer comments	This study is a case study of lampsocket workers that were exposed to both Hg and lead (both agents capable of causing neurological effects). Difficult to distinguish respective contributions of each metal to symptoms/effects. Authors note that HgU levels above 300 µg/L may be associated with clinical Hg intoxication.

Information for Dose-Response Assessment	Due to the low number of exposed subjects,and the potential for exposure to more than one neurotoxicant, this study should not be included in the dose-response assessment.

Epidemiological Study Critical Evaluation Form

Reference:	Yeates, K.O., and M.E. Mortensen. 1994. Acute and chronic neuropsychological consequences of mercury vapour poisoning in two early adolescents. J. Clin. Exper. Neuropsychology. 16(2): 209-222.
Toxicological Endpoint:	Neurological

Criteria	
Peer reviewed:	Unknown. Inquiry sent to publisher.
Type of study:	Case-study
Population(s) studied:	Accidentally exposed adolescents
Case identification/definition	
Sample size:	Two half-siblings Case 1: Fifteen year-old male Case 2: Thirteen year old female
Stratification (age, sex, etc.):	None
Control identification/definition	
Sample size:	0
Matching Criteria:	Not applicable
Group selection method:	Not applicable
Data source for group information:	Not applicable
Outcome(s) studied:	Case #1 symptoms reported: tremor, rash, hypertension, cold intolerance, diaphoresis, headache, sleep disturbance, paresthesias and anorexia. Neuropsychological evaluations included the following battery of tests just after chelation began: Weschsler Intelligence Scale for Children-Revised, language tests, verbal memory test, California Verbal Learning Test, tests of constructional and nonverbal memory skills and measures of sensory and motor function. During the follow-up testing, the tests also included line orientation (a visuoperceptual measure) and formal tests of executive functions. Case #2 symptoms reported: tremor, rash, anorexia, paresthesias, irritability, social withdrawal and emotional lability. Neuropsychological evaluations completed during initial hospitalization, after initiation of treatment and 1 year later. Same battery of tests completed as Case #1.
Exposure definition:	Unintentional exposure to mercury vapor for 3 months as a result of a mercury spill and improper clean-up.

Exposure measurement:	Mercury concentrations in urine (HgU) and blood (HgB). Mercury concentrations in air.
Duration of exposure applicable to measurement (i.e. acute, chronic):	Short-term
Exposure levels:	Mercury vapor concentrations in apartment ranged from 50 to 400 µg/m^3. HgU levels in the children's adult caretakers were reported to be 1,250 µg/L (mother) and 820 µg/L (father) (both individuals not assessed in detail during the study).
Data adjustments:	Not applicable
Results	
Relative Risk, Odd Ratio, Confidence Interval:	Not applicable
Statistics	No statistical analysis conducted. Results identified as being impaired (i.e. below 10th centile compared to national norms), as being in normal range, or as improving >/= standard deviation from diagnosis to 1 year follow-up.
Case #1 Findings	Case #1 pre-therapy HgU of 1314 µg/L, and HgB of 2.3 µg/dL. After second course of treatment, HgU dropped below 100 µg/L and remained below this level upon follow-up 1 year later. In the initial evaluation, results of information, vocabulary, digit span, picture arrangement and block design neurological tests were below average. A below average IQ was established, and the results of verbal and memory skills were consistent with the IQ observed. During follow-up 1-year later, the results of the digit span, picture arrangement, and block design improved. No significant change in performance in the Information and vocabulary tests were observed. Some improvements in verbal skills and memory were observed, however, nonverbal skills and memory were still impaired. Improvements were noted in the subjects behaviour upon neuropsychiatric evaluations between the initial visit and the follow-up.

Case #2 Findings	Case #2 pre-therapy HgU of 624 µg/L and HgB of 6.9 µg/dL. After three courses of treatment HgU dropped below 100 µg/l and remained below this level upon follow-up 1 year later. At the initial visit, the subject demponstrated various neurological effects (tremor, rash, anorexia, paresthesias, neuropsychiatric complaints. Subject was admitted to hospital for 'mercury poisoning' and acrodynia. Overall performance on neuropsychological tests were within the low-average range, with the exception of the picture arrangement test (for which the score was reduced). Verbal skills and memory, and non-verbal skills and memory were also all impaired. Corticosensory functions were unremarkable, but motor speed was impaired. At the 1-year follow up visit, improvements were noted in the picture arrangement test, verbal skills and memory, and motor speed and dexterity. Non-verbal functions, including verbal skills and verbal memory remained impaired. Improvement in the subjects behaviour during neuropsychiatric evaluation was observed between the intial and follow-up visits.
Dose response presence/absence:	Not applicable
Biases identified by the authors:	Not applicable
Assumptions/limitations of the study:	Limited number of subjects
Conclusions:	Children and adolescents may be more vulnerable to the effects of Hg vapour exposure than adults. Hg exposure may result in more extensive injury to the developing brain, potentially from diffuse and/or multifocal neurological insults.
Reviewer Comments	This article is a case study, but illustrates potential differences in effect between children, adolescents and adults. 24-hour urine collection used.

Information for Dose-Response Assessment	This study outlines two cases of unintentional mercury exposure. Due to the small sample size and the nature of exposure this study should not be included in the dose-response assessment.