

## LITERATURE REVIEW: DENTAL AMALGAM FILLINGS AND HEALTH EFFECTS

ADA Council on Scientific Affairs

### I. Preface

The last extensive review of the published literature relevant to amalgam safety was conducted by the Life Science Research Office (LSRO) and published in 2004. The LSRO expert panel report concluded that there was no consistent evidence of adverse health effects attributed to dental amalgam fillings. The panel noted that insufficient evidence was available on the topics of dental amalgam and: 1) antibiotic-resistance in human gut or oral flora; 2) pregnancy outcomes; and 3) co-exposure to organic and inorganic mercury. The Panel also noted the existence of several research gaps that, if filled, may definitively support or refute the hypothesis that dental amalgam adversely affects health.

Research gaps identified by LSRO:

- A. Well-controlled studies that use standardized measures of exposure and evaluate neurotoxic and/or neuropsychological effects and, if any, dose-response relationships.
- B. Studies examining the effects of co-exposure to organic and elemental mercury.
- C. Studies investigating the *in utero* effects of low-level elemental mercury exposure.
- D. Large occupational studies evaluating effects on reproduction and pregnancy outcomes.
- E. Studies evaluating the amount of mercury absorbed from breast milk and the effect on the developing brain.
- F. Well-controlled studies using standardized measures that investigate the incidences of kidney disease, emotional instability, erethrism, pulmonary dysfunction or other characteristics of occupational mercury exposure in dental professionals.
- G. Studies evaluating any genetic basis for sensitivity to mercury exposure.
- H. Gender differences in the pharmacokinetics and toxicity of mercury.

To identify to what extent these research gaps have been addressed, a search of the literature published between January 1, 2004 (the end point of the LSRO review) and May 2, 2008 was carried out. A search of the MEDLINE database using PubMed identified 433 articles on the topic of dental amalgam. The search was limited to *in vivo* studies on humans and those published in English. Studies were limited to human evaluations, because adverse health effects in laboratory animals do not reliably predict adverse health effects in humans. The abstracts of the 433 articles were reviewed to identify all studies relevant to amalgam and biochemical, behavioral and/or toxicological effects. Thirty-seven relevant articles were identified and summarized. Subsequently, to update the literature review on dental amalgam safety completed in May 2008 another

MEDLINE search using PubMed was conducted for the time period May 3, 2008 to April 22, 2009. The search was limited to the types of studies described above and identified 185 articles on the topic of dental amalgam. The abstracts of 185 articles were reviewed and seventeen relevant research articles were identified. The 54 studies identified from both searches are described below. Another update covered the literature published from April 23, 2009 through June 15, 2010. Using the same search strategy described above identified 205 articles. The abstracts of the 205 articles were reviewed and twelve relevant research articles were identified and are summarized below. A secondary broader search for the same time period was also conducted using PubMed to ensure that no articles were missed. Review of the search results did not reveal any additional relevant articles.

In the six years since the LSRO report was published the identified research gaps have not been completely addressed. However a number of studies have added to the growing body of literature on the topic of amalgam safety. The findings of the studies published between January 1, 2004 and June 15, 2010 showed no consistent evidence of harm associated with dental amalgam fillings, including for infants and children. There is some evidence that mercury excretion may be affected by gender. There was no evidence demonstrating that some individuals are genetically susceptible to harmful effects from exposure to the low doses of mercury associated with dental amalgam fillings. Overall, studies continue to support the position that dental amalgam is a safe restorative option for both children and adults. When responding to safety concerns it is important to make the distinction between known and hypothetical risks.

The relevant studies are summarized below and are grouped based on the research gaps identified by LSRO.

## **II. Literature Summary**

### **A. Well-controlled studies that use standardized measures of exposure and evaluate neurotoxic and/or neuropsychological effects and, if any, dose-response relationships.**

Summary: A number of well-controlled studies that evaluated neuropsychological and neurobehavioral function and exposure to amalgam fillings in children and adults are described below. Many of the studies used data generated from the Children's Amalgam Trials that evaluated exposure in hundreds of school children between the ages of 6 and 10 over a five or seven year period. These studies found no evidence that exposure to amalgam causes adverse health outcomes using a number of neurological endpoints.

#### [Amalgam exposure and neurological function.](#)

Kingman A, Albers JW, Arezzo JC, Garabrant DH, Michalek JE. *Neurotoxicology*. 2005 Mar;26(2):241-55.

This study examined 1663 dentate Vietnam era veterans participating in the Air Force Health Study. Study outcomes included clinical neurological signs, vibrotactile thresholds and summary variables for different levels of peripheral neuropathy. No significant associations were found between amalgam exposure and clinical neurological signs of abnormal tremor, coordination, station or gait, strength, sensation, or muscle stretch reflexes or for any level of peripheral neuropathy in the subjects. A significant association was detected between amalgam exposure and the continuous vibrotactile

sensation response. The authors reported that this association was a sub-clinical finding that was not associated with symptoms, clinically evident signs of neuropathy, or any functional impairment. The authors concluded that overall, there was no association between amalgam exposure and neurological signs or clinically evident peripheral neuropathy.

[Neurobehavioral effects of dental amalgam in children: a randomized clinical trial.](#)

DeRouen TA, Martin MD, Leroux BG, Townes BD, Woods JS, Leitão J, Castro-Caldas A, Luis H, Bernardo M, Rosenbaum G, Martins IP. JAMA. 2006 Apr 19;295(15):1784-92.

This article is the first published report of the children who participated in the randomized controlled trial designed to assess the safety of amalgam. A total of 507 children in Lisbon, Portugal aged 8 to 10 years received either dental amalgam or composite restorations. During the 7-year trial period children were assessed for effects on memory, attention, visuomotor function, and nerve conduction velocities. The authors concluded that children who received dental restorative treatment with amalgam did not show statistically significant differences in neurobehavioral assessments or in nerve conduction velocity compared to children who received composite fillings. The authors also reported a higher re-treatment need among the children receiving composite fillings.

[Neuropsychological and renal effects of dental amalgam in children: a randomized clinical trial.](#)

Bellinger DC, Trachtenberg F, Barregard L, Tavares M, Cernichiari E, Daniel D, McKinlay S. JAMA. 2006 Apr 19;295(15):1775-83.

This article is the first published report of the children who participated in the New England Children's Amalgam Trial that randomized 534 children ages 6 to 10 to two groups that either received dental amalgam or composite restorations. The five-year study evaluated IQ score, memory index, visuomotor composite and urinary albumin. The authors reported no statistically significant differences in neuropsychological or renal effects observed in children who had amalgam fillings placed compared to those that had composite fillings placed. The authors stated that although very small IQ effects cannot be ruled out, these findings suggest that the health effects of amalgam restorations in children need not be the basis of treatment decisions when choosing restorative dental materials.

[Dental amalgam restorations and children's neuropsychological function: the New England Children's Amalgam Trial.](#)

Bellinger DC, Daniel D, Trachtenberg F, Tavares M, McKinlay S. Environ Health Perspect. 2007 Mar;115(3):440-6. Epub 2006 Oct 30.

This randomized controlled clinical trial included 534 children (6- to 10-years old at baseline) and evaluated the effect of exposure to mercury from dental amalgam on neuropsychological function over a five-year period. Children who received dental amalgam restorations were compared to those who received composite restorations. The children had on average approximately 9 carious surfaces restored. The authors concluded that there was no difference in the neuropsychological function of the children who received dental amalgam fillings compared to the children who received composite fillings.

[A dose-effect analysis of children's exposure to dental amalgam and neuropsychological function: the New England Children's Amalgam Trial.](#)

Bellinger DC, Trachtenberg F, Daniel D, Zhang A, Tavares MA, McKinlay S. J Am Dent Assoc. 2007 Sep;138(9):1210-6.

This study describes a more sensitive analysis of the data described in the previous study. The authors examined a sample of children with substantial unmet dental needs using a dose-effect analysis. There was no significant association between neuropsychological outcomes and mercury exposure. The authors concluded that there appeared to be no detectable adverse neuropsychological outcomes in children attributable to the use of amalgam restorations.

[Neurological outcomes in children with and without amalgam-related mercury exposure: seven years of longitudinal observations in a randomized trial.](#)

Lauterbach M, Martins IP, Castro-Caldas A, Bernardo M, Luis H, Amaral H, Leitão J, Martin MD, Townes B, Rosenbaum G, Woods JS, Derouen T. J Am Dent Assoc. 2008 Feb;139(2):138-45. Erratum in: J Am Dent Assoc. 2008 Apr;139(4):404.

This randomized, prospective controlled trial examined the safety of dental amalgam. Data was collected over a seven year period of the Children's Amalgam Trial, which included 507 children from the ages of 8 through 12 years. Children received either amalgam or composite fillings and received a mean of 7.7 to 10.7 amalgam surfaces per subject over the seven years of follow-up. The investigators performed annual clinical neurological examinations that looked for both neurobehavioral and neurological effects. The authors concluded that amalgam exposure had no adverse neurological outcomes.

[Dental Amalgam and Psychosocial Status: The New England Children's Amalgam Trial.](#)

Bellinger DC, Trachtenberg F, Zhang A, Tavares M, Daniel D, McKinlay S. J Dent Res. 2008 May;87(5):470-474.

This study was part of the New England Children's Amalgam Trial that randomized 534 children ages 6 to 10 to two groups that either received dental amalgam or composite restorations. The investigators examined psychosocial outcomes using both a parent-completed Child Behavior Checklist and children's self-reports. The authors concluded that there is no evidence that exposure to mercury from dental amalgam fillings is associated with adverse psychosocial outcomes in the five-year period following amalgam placement.

[Health effects of dental amalgam exposure: a retrospective cohort study.](#)

Bates MN, Fawcett J, Garrett N, Cutress T, Kjellstrom T. Int J Epidemiol. 2004 Aug;33(4):894-902. Epub 2004 May 20.

A retrospective cohort study that included 20,000 people in the New Zealand Defence Force between 1977 and 1997. The authors investigated the association of amalgam fillings and disorders of the nervous system and kidneys. Multiple sclerosis had an adjusted hazard ratio of 1.24, but there was no association with chronic fatigue syndrome or kidney disease. There were insufficient cases for investigation of Alzheimer's or Parkinson's diseases. The authors concluded that their results provided only limited evidence of an association between amalgam and disease.

[Nephrotoxicity, neurotoxicity, and mercury exposure among children with and without dental amalgam fillings.](#)

Ye X, Qian H, Xu P, Zhu L, Longnecker MP, Fu H. Int J Hyg Environ Health. Int J Hyg Health. 2009 Jul;212(4): 378-86. Epub 2008 Nov 7.

This study evaluated the effect of low-level mercury exposure on renal function and neurobehavioral and neuropsychological performance among children 403 children aged 7-11 years in five Chinese schools. 198 children had amalgam fillings and 205 had never had dental amalgam treatment. Mean urinary mercury concentration was 1.6 µg/g creatinine for children with amalgam fillings and 1.4 µg/g creatinine for children without amalgam fillings. The authors reported no differences in either renal function, or on neurobehavioral, neuropsychological, or intelligence tests between children with and without amalgam fillings. The authors concluded that although urinary mercury concentration was slightly elevated among children with amalgam fillings, no evidence of adverse outcomes were evident. These results agree with those from recent trials in developed countries.

[Blood mercury concentrations in CHARGE study children with and without autism.](#)

Hertz-Picciotto I, Green PG, Delwiche L, Hansen R, Walker C, Pessah IN. Environmental Health Perspectives. 2010 Jan;118(1):161-6

Children from the Childhood Autism Risk from Genetics and the Environment (CHARGE) Study were selected for this study to compare blood total Hg concentrations in children with autism or autism spectrum disorder (AU/ASD) and typically developing (TD) controls. Mothers of AU/ASD children resembled those of general population controls with regards to sociodemographics. Fish consumption strongly predicted total Hg concentration, however fish consumption was less prevalent in AS/ASD children compared to TD children. After adjustment, blood Hg levels in AU/ASD children were similar to those of TD children. Children with dental amalgams and gum-chewing or teeth-grinding habits had higher blood Hg levels. Authors concluded from multiple analyses that children with AU/ASD have blood matched Hg levels comparable with those of age-matched TD controls.

[Neuropsychological function in school-age children with low mercury exposures.](#)

Surkan PJ, Wypij D, Trachtenberg F, Daniel DB, Barregard L, McKinlay S, Bellinger DC. Environ Res. 2009 Aug;109(6): 728-33.

Baseline data from the New England Children's Amalgam Trial was used to investigate potential adverse health effects of exposure to low levels of methylmercury (MeHg). Hair Hg levels from 355 children were compared with a broad range of neuropsychological endpoints. None of the neuropsychological test scores were significantly correlated with hair Hg in unadjusted analyses and no significant linear relationships were observed between hair Hg level and the neuropsychological test scores in adjusted analyses. However significant deviations from linearity were observed in the relationships between hair Hg and 2 test scores (WIAT Math Reasoning and WRAMVA Visual-Motor Composite). The authors conclude that their results suggest that hair Hg levels below 1.0 µg/g are unlikely to produce adverse neuropsychological effects in school-age children. This article only pertains to methylmercury and not elemental mercury.

[Urinary porphyrin excretion in children with mercury amalgam treatment: findings from the casa pia children's dental amalgam trial.](#)

Woods JS, Martin MD, Leroux BG, DeRouen TA, Bernardo MF, Luis HS, Leitao JG, Simmonds PL, Echeverria D, Rue TC. J Toxicol Environ Health A. 2009;72(14):891-6.

Previous studies have found that changes in the porphyrin excretion pattern may be a biomarker of occupational mercury (Hg) exposure and toxicity. The present study utilized data from the Casa Pia Children's Dental Amalgam Trial. This cohort of 507 children aged 8-12 at study inception with no preexisting neurological or developmental disabilities or amalgam restorations were randomized to amalgam or composite treatment groups and followed for seven years. Urinary porphyrins were determined in relation to Hg exposure for this cohort. No significant differences were found when comparing all subjects for any of the porphyrins of interest, but the mean concentrations of penta-, precopro-, and coproporphyrins were elevated among the amalgam group, particularly at follow-up year 3. This finding became more pronounced when restricted to the younger subjects. Treatment specific increases in penta-, precopro-, and coproporphyrins were recorded, but none of these were statistically significant. Porphyrin changes are very sensitive to Hg exposure and may be useful for risk assessment for low-level Hg exposure in children.

**B. Studies examining the effects of co-exposure to organic and elemental mercury.**

Summary: These studies did not evaluate adverse health effects, but attempted to identify relevant biomarkers and indicators of exposure.

[Childhood urine mercury excretion: dental amalgam and fish consumption as exposure factors.](#)

Levy M, Schwartz S, Dijak M, Weber JP, Tardif R, Rouah F. Environ Res. 2004 Mar;94(3):283-90.

Sixty children were studied to assess urinary mercury excretion and its relation to dental amalgam and fish consumption. Children with amalgam fillings had statistically significantly higher urinary mercury levels compared to children without amalgam fillings. The authors reported that the urinary mercury levels were also associated with fish consumption. The urinary mercury levels in the amalgam group were well below levels that are known to cause adverse health effects.

[Mercury in human brain, blood, muscle and toenails in relation to exposure: an autopsy study.](#)

Björkman L, Lundekvam BF, Laegreid T, Bertelsen BI, Morild I, Lilleng P, Lind B, Palm B, Vahter M. Environ Health. 2007 Oct 11;6:30.

The study evaluated methyl and inorganic mercury in different regions of the brain, blood, muscle and toenails in an effort to determine useful biomarkers for mercury exposure. The authors concluded that methyl mercury in blood was a useful biomarker for methyl mercury concentrations in the brain. They found no useful biomarkers for inorganic mercury in the brain. For non-occupationally exposed individuals the study found that the number of dental amalgam surfaces was an indicator of the concentration of inorganic mercury in the brain.

### **C. Studies investigating the *in utero* effects of low-level elemental mercury exposure.**

Summary: Maternal amalgam fillings result in *in utero* exposure to low levels of elemental mercury. There is no reliable evidence from controlled studies that this exposure is associated with any adverse pregnancy outcomes or health effects in the newborns and infants.

#### [Effect of amalgam fillings on the mercury concentration in human amniotic fluid.](#)

Luglie PF, Campus G, Chessa G, Spano G, Capobianco G, Fadda GM, Dessole S. Arch Gynecol Obstet. 2005 Feb;271(2):138-42. Epub 2003 Dec 20.

Seventy-two pregnant women took part in the prospective study examining the effect of the number and surface areas of amalgam fillings on the mercury concentration in amniotic fluid. The investigators found that the number and surface areas of amalgam fillings positively influenced the mercury concentrations in amniotic fluid, but not at a statistically significant level. The authors concluded that mercury levels detected in amniotic fluid were low and they observed no adverse outcomes during the pregnancies (incidence of hypertension, premature rupture of membranes, caesarean section rate, postpartum hemorrhage) or in the newborns (Apgar scores, hypocalcemia, hypoglycemia, hyperbilirubinemia, sepsis, respiratory distress syndrome, asphyxia, seizures).

#### [Maternal amalgam dental fillings as the source of mercury exposure in developing fetus and newborn.](#)

Palkovicova L, Ursinyova M, Masanova V, Yu Z, Hertz-Picciotto I. J Expo Sci Environ Epidemiol. 2008 May;18(3):326-31. Epub 2007 Sep 12.

This study assessed the relationship between maternal dental amalgam fillings and exposure of the developing fetus to mercury. The study subjects were 99 mother-child pairs. Questionnaires were completed after delivery and mercury levels in maternal and cord blood were recorded. The authors report that none of the cord blood samples contained mercury at levels considered to be hazardous for neurodevelopmental effects in children exposed to mercury *in utero* using the EPA reference dose (5.8 µg/l in cord blood). Levels of mercury in cord blood were significantly associated with the number of maternal amalgam fillings and with the number of years since the last filling. The authors concluded that dental amalgam fillings in girls and women of reproductive age should be used with caution to avoid prenatal mercury exposure.

#### [Mercury Exposure from Dental Filling Placement during Pregnancy and Low Birth Weight Risk.](#)

Hujoel PP, Lydon-Rochelle M, Bollen AM, Woods JS, Geurtsen W, del Aguila MA. Am J Epidemiol. 2005 Apr 15;161(8):734-40.

This population-based, case-control study evaluated the risk of a low birth weight pregnancy outcome associated with placement of amalgam fillings. The study was conducted by linking dental utilization data from Washington Dental Service to Vital Records birth certificates from Washington State. The study included women between the ages of 12 and 45 years with a dental treatment between January 1, 1993, and December 31, 2000. 1,117 women with low birth weight infants were compared with a

random sample of 4,468 women who gave birth to infants that were not low birth weight. 4.9% of the women had at least one amalgam filling placed during pregnancy. These women were not found to be at higher risk for a low birth weight infant and neither were women who had from 4 to 11 amalgam fillings placed.

[Maternal dental history, child's birth outcome and early cognitive development.](#)

Daniels JL, Rowland AS, Longnecker MP, Crawford P, Golding J; ALSPAC Study Team. *Paediatr Perinat Epidemiol.* 2007 Sep;21(5):448-57.

This study evaluated prenatal exposure to mercury from amalgam fillings and adverse the reproductive outcomes: preterm delivery, low birthweight and delayed neurodevelopment. Maternal dental history prior to and during pregnancy was documented for 7375 offspring born in Britain between 1991 and 1992. Nearly 90% of the women in this study received dental care during pregnancy. Of these women 31% had amalgams placed or removed. 71% of the women had 4 or more amalgams in place prior to conception. Dental care was not associated with gestational age or birthweight. The odds of term low birthweight or preterm birth were not associated with maternal history of any dental care during pregnancy or with having an amalgam filling placed or removed. Having more fillings in place at time of conception did not negatively affect pregnancy or birth outcome. Early communicative development scores were not associated with receiving dental care or with placement or removal of amalgam fillings. In addition, the odds of scoring low were not associated with maternal dental history. Although low (0.01µg/g wet weight) and not statistically significant, the mean umbilical cord mercury concentration was slightly higher in women who had dental care. However cord mercury concentrations did not differ significantly among mothers in relation to amalgam fillings during pregnancy or by the number of amalgams in place prior to pregnancy. The association between maternal dental history and offspring's communicative development was not affected when adjusted for mercury level among the subset of offspring with umbilical cord mercury data. Overall, dental amalgam fillings were not associated with birth outcomes or language development.

[A prospective study of prenatal mercury exposure from maternal dental amalgams and autism severity.](#)

Geier DA, Kern JK, Geier MR. *Acta Neurobiologiae Experimentalis.* 2009;69(2):189-97.

This study examined the relationship between *in utero* mercury exposure from maternal dental amalgams and severity of autism or an autism spectrum disorder (ASD) in 100 subjects. No control group was utilized and the study design appears to be retrospective, not prospective. The outcome (autism or ASD) was determined at the start of the study, and the exposure was ascertained from past records. After adjusting for age, gender, race, and region, the mean difference of maternal amalgams was not statistically significant between DSM-IV (severe) and ASD (mild) groups. Further analysis found that the number of maternal amalgams increased the odds of being diagnosed with autism (severe) relative to ASD (mild) however only the group with 8+ maternal amalgams were statistically significant. Changing the statistical model to determine if there were greater odds of being diagnosed with autism compared to ASD between subjects whose mothers had 5 or fewer amalgams vs. those with 6 or more resulted in a statistically significant 3.2 fold increase for the group with 6+ maternal amalgams. The authors did not control or account for maternal methylmercury exposure and did not compare the number of maternal amalgams in children with autism or ASD with healthy controls.

#### **D. Large occupational studies evaluating effects on reproduction and pregnancy outcomes.**

Summary: Only one study was identified on this topic. No significant association was found between occupational exposure to dental amalgam and miscarriage. The study does not provide adequate evidence to address this research gap.

##### [Occupational exposure in dentistry and miscarriage.](#)

Lindbohm ML, Ylöstalo P, Sallmén M, Henriks-Eckerman ML, Nurminen T, Forss H, Taskinen H. *Occup Environ Med.* 2007 Feb;64(2):127-33. Epub 2006 Oct 19

This study evaluated occupational exposures in dentistry and the risk for miscarriage. The final study population included 222 cases of miscarriage and 498 controls. Data was collected using a questionnaire. The investigators found non-significant associations between exposure to some acrylate compounds, dental amalgam, solvents, disinfectants and radiation and miscarriage. There was no dose-response relationship.

#### **E. Studies evaluating the amount of mercury absorbed from breast milk and the effect on the developing brain.**

Summary: Only one study was identified on this topic. The study reported that the presence of maternal dental amalgam fillings may expose nursing infants to mercury levels that exceed WHO's intake limit. The reported results are not in agreement with previous results from similar studies. The study does not provide adequate evidence to address this research gap.

##### [Breast-Milk Mercury Concentrations and Amalgam Surface in Mothers from Brasilia, Brazil.](#)

da Costa SL, Malm O, Dorea JG. *Biol Trace Elem Res.* 2005 Aug;106(2):145-51.

This study examined the mercury levels in human breast milk in 23 women in Brazil. The authors state that dental fillings were the primary source of inorganic mercury. The authors found a correlation between breast-milk mercury concentrations and amalgam surfaces. However, it is important to note that the correlation coefficient was low at 0.6. This means that approximately sixty percent of the variation in the response variable (mercury in milk) can be explained by the explanatory variable (amalgam surfaces). The remaining forty percent can be explained by inherent variability. The authors concluded that in 56.5% of low-fish-eating mothers, the amount of mercury likely ingested by breast-fed infants would exceed the WHO reference, which the authors state is 0.5µg/kg body weight/day. The tolerable daily intake set by the WHO is actually 2.0µg/kg body weight/day. Using this number 2 mothers (7%) had breast milk samples above WHO's intake limit. The mercury concentrations from the breast milk in this group of women are from 3 to 14 times higher than previously reported.<sup>1-4</sup> In addition, the other studies reported fish consumption as an additional source of mercury exposure. The women in this study reported eating fish on average once per month. The women in this study had on average 7 amalgam fillings. Other studies reported higher numbers of amalgam fillings. Therefore, the higher breast milk mercury concentrations in this group of women, is not explained by frequent fish consumption or a greater number of amalgam fillings.

- 1 Oskarsson A, Schutz A, Skerfving S, Hallen IP, Ohlin B, Lagerkvist BJ. Total and inorganic mercury in breast milk and blood in relation to fish consumption and amalgam fillings in lactating women. Arch Environ Health 1996;51:234-241.
- 2 Drexler H, Schaller KH. The mercury concentration in breast milk resulting from amalgam fillings and dietary habits. Environ Res. 1998;77:124-91.
- 3 Drasch G, Aigner S, Roeder G, Staiger F, Lipowsky G. Mercury in human colostrum and early breast milk. Its dependence on dental amalgam and other factors. J Trace Elem Med Biol. 1998;12:23-7.
- 4 Ursinyova M, Masanova V. Cadmium, lead and mercury in human milk from Slovakia. Food Addit Contam. 2005 Jun;22(6):579-89.

**F. Well-controlled studies using standardized measures that investigate the incidences of kidney disease, emotional instability, erethrism, pulmonary dysfunction or other characteristics of occupational mercury exposure in dental professionals.**

Summary: The two small studies on this topic were conducted via questionnaires and do not adequately address this research gap.

[Mercury vapour levels in dental practices and body mercury levels of dentists and controls.](#)

Ritchie KA, Burke FJ, Gilmour WH, Macdonald EB, Dale IM, Hamilton RM, McGowan DA, Binnie V, Collington D, Hammersley R. Br Dent J. 2004 Nov 27;197(10):625-32; discussion 621.

This study evaluated 180 dentists in West Scotland for mercury exposure and effects on their health and cognitive function. Dentists were found to have, on average, over 4 times the level of urinary mercury compared to age- and education-matched control subjects. The authors reported that, based on their questionnaire, dentists were more likely than control subjects to report having a disorder of the kidney, although this effect was not significantly associated with their urinary mercury level. An age effect was found for memory disturbances in dentists but not in the control subjects. There was no significant association between urinary mercury concentrations and self-reported memory disturbance.

[A 30-year follow-up of residual effects on New Zealand School Dental Nurses, from occupational mercury exposure.](#)

Jones L, Bunnell J, Stillman J. Hum Exp Toxicol. 2007 Apr;26(4):367-74.

This study compared the general health, reproductive health, cognition and mood of 43 ex-School Dental Service employees exposed to copper amalgam with 32 matched controls. The authors concluded that the dental nurses (average age of 52) did not appear to be neurobehaviorally compromised. The exposed group reported that they were in very good health, which was the same as the control group. The authors reported that there were seven symptoms from a list of 33 that were selected from a medical definition of mercury poisoning that were reported at a higher rate by exposed group than by the control group (arthritis, bloating, dry skin, headache, metallic taste, sleep disturbances and unsteadiness). It did not appear that the investigators performed post-hoc testing to compensate for multiple comparisons.

[Occurrence of cognitive symptoms in dental assistants with previous occupational exposure to metallic mercury.](#)

Hilt B, Svendsen K, Syversen T, Aas O, Qvenild T, Sletvold H, Melo I. *Neurotoxicology*. 2009 Nov;30(6):1202-6.

The aim of the study was to determine if dental assistants exposed to mercury have an increased prevalence of symptoms consistent with cognitive malfunction and to quantify the occurrence. A list of potential female dental assistants from 3 counties in central Norway was obtained from the public dental health care system and private practices. These 1224 women were invited to participate by filling out mailed questionnaires inquiring about symptoms regarding neurology, psychosomatics, memory, concentration, mood, sleep disturbances, and fatigue and give consent to access their urinary mercury data from the National Institute of Occupational Health if available. Of these 1224 women, 608 were included in the study and 425 unexposed women were selected as controls. No urinary Hg data was available for control subjects. Demographics for both groups were similar except for the control group having a higher level of formal education. Mean scores for single symptoms were statistically higher for dental assistants. Authors found that there was a statistically significant relationship between the maximum urine value observed and the sum of symptom scores, but statistical significance disappeared when adjusted for age. There was also a significant relationship between number of years worked and the sum of symptom scores, but again disappeared when adjusted for age. Comparison for those that had 3 or more of the symptoms was not statistically different.

[Neurological symptoms among dental assistants: a cross-sectional study.](#)

Moen B, Hollund B, Riise T. *J Occup Med Toxicol*. 2008 May 18;3:10.

This cross-sectional study assessed self-reported neurological symptoms among 41 dental assistants and 64 assistant nurses. The authors report that the dental assistants were significantly older, had more years at work, and higher alcohol consumption than the assistant nurses. Based on the results of a mail survey, the study found that the dental assistants, who were assumed to have occupational exposure to mercury, had significantly higher occurrences of neurological symptoms, psychosomatic symptoms, memory deficit, concentration, fatigue and sleep disturbance than the assistant nurse group. They found the largest effect to be on memory. There was no specific information on exposure to mercury for either group (dental assistants vs. nurses), and, therefore the authors state that the results should be interpreted with caution.

**G. Studies evaluating any genetic basis for sensitivity to mercury exposure.**

Summary: Studies evaluating exposure effects in individuals that are reportedly sensitive to mercury did not show consistent evidence that a sensitive group exists. In addition, no specific genotoxic effects were found associated with exposure to amalgam.

[The beneficial effect of amalgam replacement on health in patients with autoimmunity.](#)

Prochazkova J, Sterzl I, Kucerova H, Bartova J, Stejskal VD. *Neuro Endocrinol Lett*. 2004 Jun;25(3):211-8.

This study evaluated thirty-five patients described as mercury-allergic with autoimmunity that had their amalgam fillings replaced with composite fillings and ceramic materials. The authors evaluated self-reported health status and lymphocyte reactivity. The authors reported that 71% of patients experienced health improvements and that the patients who improved were the ones with the highest lymphocyte reactivity before amalgam removal. The conclusion was that mercury-containing amalgam may be an important risk factor for patients with autoimmune diseases and that lymphocyte reactivity is a valuable tool for selection of patients for amalgam replacement. The study did not include a control group.

[Treatment of health complaints attributed to amalgam.](#)

Melchart D, Vogt S, Köhler W, Streng A, Weidenhammer W, Kremers L, Hickel R, Felgenhauer N, Zilker T, Wühr E, Halbach S. J Dent Res. 2008 Apr;87(4):349-53.

This randomized and controlled study compared the reduction of subjective complaints in 90 “amalgam patients” using three treatment strategies. Individuals were randomly assigned to have their amalgams removed only, to have their amalgams removed with “biological detoxification” therapy or to participate in a health promotion program without dental amalgam removal. Observations were made for 18 months. Mercury in erythrocytes, blood and urine were evaluated. Mercury concentrations in the removal groups were significantly different from the non-removal group in blood and urine, but not in erythrocytes. An improvement in subjective health complaints was found in all three groups.

[Biomonitoring of mercury in patients with complaints attributed to dental amalgam, healthy amalgam bearers, and amalgam-free subjects: a diagnostic study.](#)

Melchart D, Köhler W, Linde K, Zilker T, Kremers L, Saller R, Halbach S. Clin Toxicol (Phila). 2008 Feb;46(2):133-40.

This report describes an investigation into the suitability of using mercury levels as a means of identifying patients with health complaints attributed to dental amalgam. Mercury levels in erythrocytes, plasma, urine, and saliva were determined in 27 patients complaining about health problems attributed to amalgam, 27 healthy volunteers with amalgam fillings, and 27 healthy amalgam-free volunteers. The investigators found that concentrations of inorganic mercury in blood and of total mercury in urine and saliva differed significantly between individuals with amalgam fillings and amalgam-free volunteers, but not between symptomatic patients and healthy volunteers with amalgam fillings. Levels of organic mercury were equal in all groups. The authors concluded that concentrations of total and inorganic mercury in body fluids do not distinguish between asymptomatic amalgam bearers and those who suffer from a poorly defined syndrome of multiple nonspecific symptoms.

[Four years of clinical experience with an adverse reaction unit for dental biomaterials.](#)

Vamnes JS, Lygre GB, Grønningsaeter AG, Gjerdet NR. Community Dent Oral Epidemiol. 2004 Apr;32(2):150-7.

This study describes the findings from 296 patients examined at the Norwegian National Dental Biomaterials Adverse Reaction Unit from 1993 to 1997. Dental amalgam was the primary reason for referral. Patients reported general subjective symptoms, such as muscle and joint pain, fatigue, memory problems and orofacial symptoms. The

investigators found no significant correlation between mercury concentrations in blood and urine and the number of subjective symptoms or objective findings.

[A 7-year prospective quasi-experimental study of the effects of removing dental amalgam in 76 self-referred patients compared with 146 controls.](#)

Nerdrum P, Malt UF, Høglend P, Oppedal B, Gundersen R, Holte M, Löne J. J Psychosom Res. 2004 Jul;57(1):103-11.

This quasi experimental study evaluated changes in mental and physical symptoms in 76 patients who had their dental amalgam removed 7 years prior to the evaluation. These individuals were compared with patients with known chronic medical disorders seen in alternative (n=51) and ordinary (n=51) medical family practices and non symptomatic patients with dental amalgam fillings (control group, n=44). Removal of amalgam reduced the reported physical and mental symptoms to the level of the group with known chronic medical disorders. The control group consistently reported fewer symptoms. The authors concluded that their findings did not support the hypothesis that removal of amalgam will reduce health complaints to normal levels.

[Changed Clinical Chemistry Pattern in Blood After Removal of Dental Amalgam and other Metal Alloys Supported by Antioxidant Therapy.](#)

Frisk P, Danersund A, Hudecek R. Biol Trace Elem Res. 2007;120:163-70.

This study examined clinical chemistry patterns in patients with complaints related to amalgam restorations. All 24 patients with complaints had their amalgams removed and were treated with antioxidants at unspecified doses (vitamin B-complex, vitamin C, vitamin E, and sodium selenite). The authors reported that the clinical chemistry patterns before and after amalgam removal were significantly different. The authors also reported that individuals' clinical chemistry patterns before amalgam removal were significantly different from an age- and sex-matched control group. The authors concluded that the individuals clinical chemistry patterns could be used to identify individuals based on amalgam removal. The authors did not report on any associated health effects.

[Mercury toxicity presenting as chronic fatigue, memory impairment and depression: diagnosis, treatment, susceptibility, and outcomes in a New Zealand general practice setting \(1994-2006\).](#)

Wojcik DP, Godfrey ME, Christie D, Haley BE. Neuro Endocrinol Lett. 2006 Aug;27(4):415-23.

This study describes a group of 465 patients who were given a diagnosis of chronic mercury toxicity (CMT) based on chronic physical and mental symptoms that were previously undiagnosed. The investigators found a correlation between CMT and the Apo-lipoprotein E4 genotype, which they suggest identifies a significant risk for developing Alzheimer's disease in these individuals. The individuals diagnosed with CMT had their amalgams removed and underwent chelation therapy. The authors reported that treated individuals had significant reductions in symptoms to the level reported by healthy individuals. The study design did not include randomization or blinding.

[A follow-up study of patients with subjective symptoms related to dental materials.](#)

Lygre GB, Gjerdet NR, Björkman L. Community Dent Oral Epidemiol. 2005 Jun;33(3):227-34.

This study evaluated changes in the intensity of subjective symptoms after replacement of dental materials in patients referred to the Dental Biomaterials Adverse Reaction Unit in Norway for adverse reactions to dental materials. Of 142 patients, follow-up questionnaires were completed by 84 patients (3 were not included because the questionnaire was incomplete) and compared to 442 individuals in the general population (control group). Patients who had replaced dental materials (n=35) continued to report higher symptom indices than individuals in the control group. Patients who had not replaced dental materials (n=46) did not report any reduction in intensity of symptom indices. The authors concluded that the intensity of local (in the mouth) and some general subjective symptoms was reduced after dental materials were replaced, but not to the level reported by the general population.

[Biomonitoring of DNA damage in peripheral blood lymphocytes of subjects with dental restorative fillings.](#)

Di Pietro A, Visalli G, La Maestra S, Micale R, Baluce B, Matarese G, Cingano L, Scoglio ME. *Mutat Res.* 2008 Feb 29;650(2):115-22. Epub 2007 Nov 22.

This study evaluated the genotoxicity of dental restorative materials. The investigators evaluated blood specimens from 68 subjects (44 exposed to either or both dental amalgam and composites). DNA damage was assessed using the comet assay and the investigators concluded that both amalgam and methacrylates trigger the generation of cellular reactive oxygen species that cause oxidative DNA lesions.

[Mercury exposure in dental practice.](#)

Atesagaoglu A, Omurlu H, Ozcagli E, Sardas S, Ertas N. *Oper Dent.* 2006 Nov-Dec;31(6):666-9.

This study evaluated the genotoxicity of occupational exposure to mercury in 10 dentists. The authors concluded that blood samples taken from dentists exposed to mercury vapor concentrations below 0.1mg/m<sup>3</sup> did not exhibit cytogenetic damage to leukocytes.

[The association between serotonin transporter gene promoter polymorphism \(5-HTTLPR\) and elemental mercury exposure on mood and behavior in humans.](#)

Echeverria D, Woods JS, Heyer NJ, Martin MD, Rohlman DS, Farin FM, LiT. *J Toxicol Environ Health A.* 2010 Jan;73(15): 1003-20

This study evaluated the effect of elemental mercury exposure and a polymorphism in the serotonin transporter gene promoter on mood and behavior using 32 behavioral tests in dentists and dental assistants. The original pool of study participants were recruited in Washington State between 1998 and 2001, and included 193 male dentists and 230 female dental assistants. This study reports results for 164 dentists and 101 dental assistants. The authors do not explain why a large number of subjects from the original pool were excluded. The authors concluded that their results confirm that the variant for the serotonin transporter gene promoter is highly associated with subjects' mood and that this is independent of mercury exposure. However, a recent meta-analysis does not support this finding and reports that there is no evidence that the serotonin transporter genotype is associated with an elevated risk of depression in men alone, women alone, or in both sexes combined.<sup>1</sup> The authors also reported that mercury exposure combined with the polymorphism affected performance scores in sustained attention and

perception in dentists and assistants, and scores in cognitive flexibility and reaction time in dentists. This study did not include a control population.

1. Risch N, Herrell R, Lehner T, Liang KY, Eaves L, Hoh J, Griem A, Kovacs M, Ott J, Merikangas KR. Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: a meta-analysis. *JAMA*. 2009;301(23):2462-71.

[Catechol O-methyltransferase \(COMT\) VAL158MET functional polymorphism, dental mercury exposure, and self-reported symptoms and mood.](#)

Heyer NJ, Echeverria D, Martin MD, Farin FM, Woods JS. *J Toxicol Environ Health A*. 2009;72(9):599-609.

This study evaluated gene polymorphisms known to affect mood and behavior and their relationship to urinary mercury levels and self-reported neurological symptoms and mood. The study subjects were 183 male dentists and 211 female dental assistants. No associations between mercury exposure and self-reported symptoms were found in this study. The authors also reported that there were no clear groupings of symptoms associated with mercury exposures while controlling for the polymorphisms. The authors did report that symptoms were associated with polymorphisms and concluded that these results provide evidence for genetic factors potentially affecting human susceptibility to the toxic effects of mercury and other environmental chemicals – although no toxic effects were identified in this study. Although genetic polymorphisms were associated with self-reported neurological symptoms, the study did not find an association with urinary mercury levels.

#### **H. Gender differences in the pharmacokinetics and toxicity of mercury.**

Summary: One study reported a possible gender difference related to mercury excretion. However, there were no adverse health effects associated with this gender difference. More studies are needed to determine if a gender difference exists.

[The contribution of dental amalgam to urinary mercury excretion in children.](#)

Woods JS, Martin MD, Leroux BG, DeRouen TA, Leitão JG, Bernardo MF, Luis HS, Simmonds PL, Kushleika JV, Huang Y. *Environ Health Perspect*. 2007 Oct;115(10):1527-31.

This randomized controlled clinical trial included 507 children (8- to 10-years old at baseline) and evaluated the effect of exposure to mercury from dental amalgam on urinary mercury excretion. The authors report that urinary mercury concentrations were highly correlated with both the number of amalgam fillings and the time since placement in children. The authors also found that girls excrete significantly higher concentrations of mercury in urine than boys with comparable treatment. This finding suggests that there may be sex-related differences in mercury excretion.

*The studies summarized below were not relevant to a specific research gap identified by LSRO, but add to the body of knowledge on the topic of amalgam safety.*

#### **Study evaluating the influence of amalgam fillings on antibiotic-resistant bacteria in the gut and the mouth.**

Summary: No evidence was found to support the hypothesis that amalgam fillings are associated with antibiotic-resistant bacteria in the gut or mouth.

[Dental Amalgam and Antibiotic- and/or Mercury-resistant Bacteria.](#)

Roberts MC, Leroux BG, Sampson J, Luis HS, Bernardo M, Leitão J. J Dent Res. 2008 May;87(5):475-9.

This study examined the association between the presence of amalgam fillings and antibiotic- or mercury-resistant bacteria in the mouth. Participants of the study were a subset of the children who participated in the randomized controlled trial designed to assess the safety of amalgam (Children's Amalgam Trial). 150 children were included in the study designed to detect a half log change in bacteria levels with 15% drop out. The authors concluded that there was no evidence that amalgam fillings influenced the level of antibiotic- or mercury-resistant bacteria in the mouth or urine.

**Kidney function and exposure to amalgam fillings.**

Summary: Amalgam exposure had no effect on a number of markers of glomerular and tubular kidney function in over 500 children over a five-year period, except for microalbuminuria (the incidence of which was higher in the amalgam group). More studies are needed to determine if this is a consistent finding.

[Renal effects of dental amalgam in children: the New England children's amalgam trial.](#)

Barregard L, Trachtenberg F, McKinlay S. Environ Health Perspect. 2008 Mar;116(3):394-9.

This randomized, prospective controlled trial examined the safety of dental amalgam in children who received either amalgam or composite fillings. Data was collected over a five year follow-up period of the Children's Amalgam Trial, which included 534 children from the ages of 6 through 10 years. The investigators assessed changes on markers of glomerular and tubular kidney function and urinary mercury levels. The authors found no significant differences between the treatment groups and no significant effects related to the number of dental amalgam fillings on the markers. Children in both treatment groups experienced microalbuminuria, but the prevalence was higher in the amalgam group. The authors concluded that the increase in microalbuminuria may be random, but should be further evaluated.

[Nephrotoxicity, neurotoxicity, and mercury exposure among children with and without dental amalgam fillings.](#)

Ye X, Qian H, Xu P, Zhu L, Longnecker MP, Fu H. Int J Hyg Environ Health. 2009 Jul;212(4):378-86. Epub 2008 Nov 7.

This study evaluated the effect of low-level mercury exposure on renal function and neurobehavioral and neuropsychological performance among children 403 children aged 7-11 years in five Chinese schools. 198 children had amalgam fillings and 205 had never had dental amalgam treatment. Mean urinary mercury concentration was 1.6 µg/g creatinine for children with amalgam fillings and 1.4 µg/g creatinine for children without amalgam fillings. The authors reported no differences in either renal function, or on neurobehavioral, neuropsychological, or intelligence tests between children with and without amalgam fillings. The authors concluded that although urinary mercury concentration was slightly elevated among children with amalgam fillings, no evidence of

adverse outcomes were evident. These results agree with those from recent trials in developed countries.

[Biomarkers of kidney integrity in children and adolescents with dental amalgam mercury exposure: findings from the Casa Pia children's amalgam trial.](#)

Woods JS, Martin MD, Leroux BG, DeRouen TA, Bernardo MF, Luis HS, Leitão JG, Kushleika JV, Rue TC, Korpak AM. Environ Res. 2008 Nov;108(3):393-9. Epub 2008 Aug 21.

This study assessed urinary concentrations of glutathione S-transferases (GSTs)  $\alpha$  and  $\pi$ , biomarkers of renal proximal and distal tubular integrity, respectively, and albumin a biomarker of glomerular integrity, in children and adolescents 8–18 years of age over a 7-year course of dental amalgam treatment. Five hundred seven children, 8–12 years of age at baseline, participated in a clinical trial to evaluate the neurobehavioral and renal effects of dental amalgam in children. Subjects were randomized to receive either dental amalgam or resin composite restorations. Urinary GSTs  $\alpha$  and  $\pi$ , albumin, and creatinine concentrations were measured at baseline and annually in all subjects. GST  $\alpha$  and albumin concentrations were similar between treatment groups (amalgam vs. composite). GST  $\pi$  levels tended upward over the course of follow-up by four- to six-fold. This increase was seen in all groups irrespective of the treatment. The authors found no significant effects of amalgam treatment on the proportion of children with microalbuminuria (430 mg/g creatinine). The authors concluded that their findings suggest no deleterious effects of mercury exposure from dental amalgam on kidney function.

[Urinary mercury and biomarkers of early renal dysfunction in environmentally and occupationally exposed adults: a three country study.](#)

Jarosinska D, Horvat M, Sallsten G, Mazzolai B, Dabkowska B, Prokopowicz A, Biesiada M, Barregard L. Environ Res. 2008 Oct;108(2):224-232.

This cross-sectional study assessed exposure to mercury and the possible correlation to biological markers of kidney dysfunction in people living near and working in chloralkali plants in Italy, Poland, and Sweden. Questionnaire data and urine samples were collected from 757 subjects including the reference groups. Urine was analyzed for mercury corrected for creatinine (U-HgC), alpha-1-microglobulin (A1M), *N*-acetyl- $\beta$ -glucosaminidase (NAG), and albumin. Urinary mercury in the general population differed by country. Italy had the highest median value at 1.2  $\mu\text{g/gC}$  followed by Poland (0.22  $\mu\text{g/gC}$ ) and Sweden (0.21  $\mu\text{g/gC}$ ). No statistically significant difference for urinary mercury in subjects living near chloralkali plants compared to the reference group was found. Urinary mercury was higher in subjects with dental amalgam. The authors also recognized a positive association between chewing and/or fish consumption on urinary mercury. No statistically significant associations were found between urinary mercury and kidney biomarkers for the three countries in the general population. However for occupationally exposed men, urinary mercury was positively associated with A1M, albumin, and especially NAG. No conclusions were drawn regarding health effects or biomarkers in relation to elevated levels of urinary mercury in subjects with dental amalgams.

[Cadmium, mercury, and lead in kidney cortex of living kidney donors: Impact of different exposure sources.](#)

Barregard L, Fabricius-Lagging E, Lundh T, Molne J, Wallin M, Olausson M, Modigh C, Sallsten G. Environ Res. 2010 Jan;110(1): 47-54

Cadmium (Cd), mercury (Hg), and lead (Pb) are nephrotoxic metals. Most information on kidney concentration of these metals comes from autopsy studies. This study examined kidney concentrations of Cd, Hg, and Pb in 109 living kidney donors and assessed the associations with common exposure sources and background factors. Median kidney concentrations were 12.9 µg/g Cd, 0.21 µg/g Hg, and 0.08 µg/g Pb. Kidney Cd concentrations increased with age and smoking. Kidney Hg increased by 6% for every additional amalgam surface, but was not associated with fish consumption. Lead was unaffected by the background factors surveyed.

**Two systematic reviews (one with meta-analysis) examining the association between dental amalgam and health effects.**

Summary: Two systematic reviews evaluated neurological outcomes and exposure to amalgam fillings. No statistically significant associations were found for amalgam exposure and multiple sclerosis in adults and neurobehavioral and neuropsychological scores in children.

[Dental amalgam and multiple sclerosis: a systematic review and meta-analysis.](#)

Aminzadeh KK, Etminan M. J Public Health Dent. 2007 Winter;67(1):64-6. Review.

This meta-analysis evaluated the association between dental amalgam restorations and multiple sclerosis. A systematic search for data published between 1966 to April 2006 was conducted using Medline, EMBASE and the Cochrane library. The authors report finding four observational studies (three case control studies and one cohort study) that met their inclusion criteria. A meta-analysis revealed a slight nonstatistically significant increase between the presence of amalgam fillings and MS. The study does not provide evidence for or against an association.

[Mercury released from amalgam restorations does not give rise to toxic effects on the nervous system of children.](#)

Rasines G. Evid Based Dent. 2008;9(1):25-7.

This systematic review examined whether or not placement of amalgam restorations increase the risk of neuropsychological disorders compared to composite restorations in children between the ages of 6 and 10. The author included 3 clinical studies and concluded that there is no significant statistical association between the neurobehavioral and neuropsychological scores of children with amalgam versus composite fillings.

**A review examining the association between dental amalgam and autism.**

[A comprehensive review of mercury provoked autism.](#)

Geier DA, King PG, Sykes LK, Geier MR. Indian J Med Res. 2008 Oct;128(4):383-411. Review.

The article is a selective review of the literature that presents no new evidence. The conclusion of this review is that “the overwhelming preponderance of the evidence favors acceptance that Hg exposure is capable of causing some autism spectrum disorders.”

### **Studies evaluating the mercury dose absorbed from amalgam fillings.**

Summary: Studies consistently demonstrated that exposure to amalgam fillings results in absorption of elemental mercury by the body. Overall, the results are similar to previous reports.

#### [Blood and urine mercury levels in adult amalgam patients of a randomized controlled trial: Interaction of Hg species in erythrocytes.](#)

Halbach S, Vogt S, Köhler W, Felgenhauer N, Welzl G, Kremers L, Zilker T, Melchart D. Environ Res. 2008 May;107(1):69-78. Epub 2007 Sep 4.

This study evaluated the internal exposure to amalgam-related mercury and estimated the amalgam-related absorbed dose of mercury. The integrated mercury dose absorbed from amalgam fillings was estimated at up to 3 µg per day for an average number of fillings and 7.4 µg per day for a high amalgam load. The authors concluded that these estimates are well below the tolerable dose of 30 µg per day established by WHO.

#### [Dental amalgam exposure and urinary mercury levels in children: the New England Children's Amalgam Trial.](#)

Maserejian NN, Trachtenberg FL, Assmann SF, Barregard L. Environ Health Perspect. 2008 Feb;116(2):256-62.

This study examined the associations between various detailed amalgam exposure measures and urinary mercury in 267 children participating in the Children's Amalgam Trial. The authors reported that the current total of amalgam surfaces was the most robust predictor of current urinary mercury concentration. The study was not designed to examine amalgam safety.

#### [Scalp hair and urine mercury content of children in the Northeast United States: The New England Children's Amalgam Trial.](#)

Dunn JE, Trachtenberg FL, Barregard L, Bellinger D, McKinlay S. Environ Res. 2008 May;107(1):79-88. Epub 2007 Oct 24.

This analysis of data collected over the five year period of the Children's Amalgam Trial, which included 507 children from the ages of 8 through 12 years, reports mean hair mercury levels of 0.3-0.4 µg/g and mean urinary mercury levels of 0.7-0.9 µg/g creatinine. The authors report that the use of chewing gum in the presence of amalgam fillings was a predictor of higher urinary mercury levels. The urinary mercury levels in these children are similar to the mean urinary mercury levels in adult females in the U.S. according to the CDC's NHANES data.

#### [Dental amalgam and mercury levels in autopsy tissues: food for thought.](#)

Guzzi G, Grandi M, Cattaneo C, Calza S, Minoia C, Ronchi A, Gatti A, Severi G. Am J Forensic Med Pathol. 2006 Mar;27(1):42-5.

This study examined the association between mercury levels in brain tissue from 18 cadavers and the number of occlusal dental amalgam fillings. The authors report that mercury levels increased with the number of dental amalgam fillings for all tissues and that mercury levels were significantly higher in brain tissues compared with thyroid and kidney tissues in subjects with more than 12 occlusal amalgam fillings, but not in subjects with 0 to 3 occlusal amalgam fillings. The authors also stated that the levels of mercury were higher in all tissues in cases of suicide compared to non-suicides. The authors did not have accurate information on fish consumption. Individual data was not presented and the data on the association between higher mercury levels and suicide was not presented. The study did not use controls.

### **Hypersensitivity to amalgam**

**Summary:** A number of studies examined the link between amalgam fillings and localized inflammation and allergic reactions. Studies report cases of both delayed hypersensitivity that resolved with or without amalgam filling removal, and a rare immediate hypersensitivity reaction that required amalgam removal. Studies evaluating the association between oral lichen planus and amalgam fillings report contradictory findings – one concluding that an association exists and the other finding no association.

#### [Burning mouth syndrome possibly linked with an amalgam tattoo : clinical and ultrastructural evidence.](#)

Donetti E, Bedoni M, Guzzi G, Pigatto P, Sforza C. Eur J Dermatol. 2008 Nov-Dec;18(6):723-4.

This case report describes a patient who developed burning mouth syndrome following extraction of a tooth containing amalgam. The patient reportedly developed an amalgam tattoo following the extraction. The authors report that the tattoo was associated with local inflammation and pain. The patient reported an allergy to nickel. The paper describes a single report of a local inflammatory response and pain possibly associated with one or more of the metal components of amalgam.

#### [An unusual case of immediate hypersensitivity reaction associated with an amalgam restoration.](#)

Kal BI, Evcin O, Dundar N, Tezel H, Unal I. Br Dent J. 2008 Nov 22;205(10):547-50.

This case report describes an immediate hypersensitivity reaction associated with the mercury component of amalgam restorations. The authors report that the mercury from amalgam fillings induced an acute reaction which resulted in erythematous lesions, severe burning and itchy sensation and difficulty in breathing. The amalgam restorations were replaced with composite restorations and the symptoms resolved. Follow-up skin patch test results indicated a very strong positive reaction to mercury. Rare instances of delayed, localized allergic reactions have been reported in the literature. This report describes an extremely rare case of an immediate allergic reaction.

#### [Mercury sensitisation: review, relevance and a clinical report.](#)

Bains VK, Loomba K, Loomba A, Bains R. Br Dent J. 2008 Oct 11;205(7):373-8. Review.

This paper reviews the literature on hypersensitivity to mercury leading to dermatitis or type IV delayed hypersensitivity reactions most often affecting the skin (rash). The

authors report that mercury allergy is rare. Less than 2% of patients react to amalgam in patch testing and 37% of them were found to be allergic to mercury.

[Metal allergens of growing significance: epidemiology, immunotoxicology, strategies for testing and prevention.](#)

Forte G, Petrucci F, Bocca B. *Inflamm Allergy Drug Targets*. 2008 Sep;7(3):145-62. Review.

This paper describes allergies to various metals. The authors summarize amalgam allergy as follows:

“Symptoms of an amalgam allergy include skin rashes in the oral, head and neck area, itching, swollen lips, localized eczema-like lesions in the oral cavity. These clinical signs usually require no treatment and will disappear on their own within a few days of exposure. However, in some instances, an amalgam filling will have to be removed and replaced with a filling made of another restorative material, such as resin or porcelain even if these substances are more expensive and less pliable than amalgam. In patients showing positive patch test reactions with Hg-compounds, the placement or removal of amalgam fillings has led to significant improvements.”

[Association between oral lichenoid reactions and amalgam restorations.](#)

Pezelj-Ribarić S, Prpić J, Miletić I, Brumini G, Soskić MS, Anić I. *J Eur Acad Dermatol Venereol*. 2008 Nov;22(10):1163-7. Epub 2008 Apr 3.

This study examined the association between oral lichenoid reactions (OLR) and amalgam restorations in 20 patients with OLR compared to 20 healthy volunteers. Study subjects were skin patch tested and salivary levels of IL-6 and IL-8 were measured. Sixteen out of 20 patients demonstrated a contact allergy to inorganic mercury or amalgam. IL-6 and IL-8 levels were significantly elevated in the OLR group compared to the health volunteer group. The authors did not report exposure to any other drugs which may have caused the localized allergic reaction. All patients with OLR had their amalgam restorations replaced. The authors report that 16 patients experienced complete healing of their lesions, 3 showed a marked improvement and 1 showed no improvement. IL-6 and IL-8 levels reportedly dropped significantly following amalgam replacement. The follow-up was from 3 months to 3.5 years after amalgam replacement. The subjects all had their fillings replaced (there was no control group with OLR and no treatment). Therefore it's possible that the lesions resolved on their own and not as a result of amalgam removal. The authors concluded that OLR is associated with a localized allergic reaction to the mercury in amalgam fillings.

[Do metal restorations in mouth alter clinical and histological appearance of oral lichen planus?](#)

López-Jornet P, Camacho-Alonso F. *N Y State Dent J*. 2008 Nov;74(6):40-3.

This study examined whether or not clinical and histopathological differences exist between patients with oral lichen planus (OLP) who have dental amalgam fillings compared to patients without amalgam fillings. The study involved 213 patients with OLP. In both groups, OLP was found most frequently on the buccal mucosa with bilateral presentation. The researchers found no clinical or histopathological statistically significant differences between patients with OLP with or without dental amalgam.

[Oral lichenoid reaction associated with tin component of amalgam restorations: a case report.](#)

Aggarwal V, Jain A, Kabi D. American Journal of Dermatopathology. 2010 Feb;32(1):46-8.

This case report describes a twenty three year old man with bilateral oral lichenoid reaction. Histopathological features were compatible with lichenoid mucositis. Patch test resulted in positive response to amalgam powder and tin. The amalgam restorations were removed and the teeth were restored with a temporary material which was eventually replaced with a light-cured composite resin. The lesion was resolved after one month and was still absent at the six month review.

[Investigation of contact allergy to dental metals in 206 patients.](#)

Raap U, Stiesch M, Reh H, Kapp A, Werfel T. Contact Dermatitis. 2009 Jun;60(6):339-43.

This retrospective study assessed the correlation between positive patch test reactions to metals used in dentistry with clinical symptoms. Of the 206 patients who underwent patch testing from June 2003 through March 2008, 28 showed a positive patch test reaction to a dental metal. 27 of the 28 positive were female. The most frequent oral manifestation of the 28 patients was lichen planus (n=9). Oral stomatitis was also diagnosed in 8 patients. Five other different oral manifestations were also recognized. Patch test reactions were highest for gold sodium thiosulfate (n=10), palladium chloride (n=10), and nickel sulfate (n=10), followed by amalgam, ammoniated mercury, cobalt chloride, amalgam-mixed metals, and ammonium tetrachloroplatinate. Clinical relevance was defined by specific morphological symptoms in the oral cavity together with a positive patch test reaction to dental metals or dental alloys containing the suspected contact allergen in the dental fillings. This was the case for 7 of 9 patients with oral lichen planus and 7 of 8 patients with stomatitis. 49 of the 206 patients had clinical manifestations of oral lichen planus. Seven of these had a positive patch test with clinical relevance. Thus, less than 15% of the cases of oral lichen planus could have been the result of a contact allergy. Thirty two of the 206 patients who underwent patch testing had stomatitis. Seven (22%) of these had a clinically relevant positive patch test reaction.

### **Subjective complaints**

Summary: There is no evidence that individuals with perceived chronic mercury toxicity have higher levels of blood and urinary mercury, or that dental amalgam exposure is associated with multiple sclerosis or another autoimmune disease.

[Relationship between mercury levels in blood and urine and complaints of chronic mercury toxicity from amalgam restorations.](#)

Eyeson J, House I, Yang YH, Warnakulasuriya KA. British Dental Journal 2010;208(4):162-3.

The aim of this study was to determine if patients complaining of medical symptoms perceived to be associated with chronic mercury toxicity have elevated mercury levels in their blood and urine. Fifty six patients with symptoms perceived to be caused by mercury toxicity from their amalgam fillings were included in the study. A review of clinic

notes and medical histories, skin patch testing for any participant with oral lichenoid reactions, and blood and urine mercury testing were completed. None of the subjects had elevated mercury levels above the threshold level. Of the subjects patch tested, only one was found to be positive. The authors reported that the response was to mercury amalgam. Relatively higher blood mercury levels were found in subjects presenting with complaints of symptoms in the oral cavity compared to the other study subjects, but within the threshold values. These levels remained significant after adjusting for age and gender. Blood and urine mercury levels of two patients with MS were significantly higher than those without. Number of amalgams was correlated to subjects reporting autoimmune diseases. However, logistic regression adjusted for age and gender found that Hg levels in blood or urine, or number of amalgams was not significant for MS or previously diagnosed autoimmune disease. All of the 56 subjects with perceived chronic mercury toxicity were within the normal blood and urine mercury range.

[Amalgam dental fillings and hearing loss.](#)

Rothwell JA, Boyd PJ. *Int J Audiol.* 2008 Dec;47(12):770-6.

Thirty nine women between the ages of 40 and 45 made up the study population. The authors reported that an increase in the number of amalgams (range 0 to 16, mean 7.1) was associated with poorer high frequency hearing thresholds (expressed in dB HL) at 8, 11.2, 12.5, 14, and 16 kHz. The greatest correlation was at 14 kHz (n=39, p<0.001,  $r^2=0.35$ , F=19.5), where each amalgam was associated with a 2.4 dB decline in hearing sensitivity. Using ASHA's (1994) criteria of change ( $\geq 20$  dB at a single frequency), the authors reported an ototoxic effect in subjects with nine or more amalgam fillings and claim to have shown a dose-dependent effect of amalgam fillings on health in the general population. However, some study weaknesses would seem to prohibit the authors from drawing such a firm conclusion. Hearing loss is associated with ear infections and noise exposure. Neither of these variables was evaluated in the study population. Methyl mercury exposure from fish consumption was not considered. The authors relied on the number of drilling episodes (one episode per new filling or reported filling change) rather than duration of drilling to control for any effect of noise associated with drilling on hearing threshold. It's possible that amalgam restorations were associated with larger posterior fillings that could require longer drilling times.

[Caution and causation: lessons from the delicate story of dental amalgam.](#)

Williams D. *Med Device Technol.* 2008 Sep;19(5):8, 10-1.

This article is a review of the literature on amalgam safety that presents no new information. The author concludes that there is no scientific evidence to support the assertion that amalgam causes adverse health effects.

### **Longevity**

Summary: One large clinical study found that the need for replacement of composite and compomer restorations was significant higher than for amalgam fillings.

[Extent of tooth decay in the mouth and increased need for replacement of dental restorations: the New England Children's Amalgam Trial.](#)

Trachtenberg F, Maserejian NN, Tavares M, Soncini JA, Hayes C. *Pediatr Dent.* 2008 Sep-Oct;30(5):388-92.

This study evaluated the relationship between baseline caries experience and the restoration replacement rate in children participating in the New England Children's Amalgam Trial. Over the 5-year trial, 3,604 restorations with follow up were placed in 489 children (1,471 amalgam, 1,229 compomer, and 904 composite). Of the restorations, 61% were in primary teeth and 39% were in permanent teeth, with 92% in posterior teeth and 800 in anterior teeth. The authors reported that the need for replacement was significantly higher for composite and compomer resin than for amalgam restorations ( $P=0.048$ ).

### **Sources and level of exposure**

Summary: Other studies evaluated exposure levels and sources. None found any health effects associated with exposure to mercury from amalgam fillings.

#### [Mercury vapour \(Hg\(0\)\): Continuing toxicological uncertainties, and establishing a Canadian reference exposure level.](#)

Richardson GM, Brecher RW, Scobie H, Hamblen J, Samuelian J, Smith C. Regul Toxicol Pharmacol. 2009 Feb;53(1):32-8.

This study sponsored by Health Canada was a review of the literature in an attempt to establish a reference exposure level (REL) for elemental mercury. No new data was presented in this study. The authors proposed a new REL of  $0.06 \mu\text{g}/\text{m}^3$  for continuous air exposure. This is below established limits of  $0.3 \mu\text{g}/\text{m}^3$  (EPA),  $0.2 \mu\text{g}/\text{m}^3$  (ATSDR) and  $1.0 \mu\text{g}/\text{m}^3$  (WHO). The proposed REL is 100 times below the lowest-observed-adverse-effect-level (LOAEL). The authors concluded that this daily dose limit may be achieved from the presence of no more than three amalgam fillings in toddlers and five amalgam fillings in adults ( $0.2 \mu\text{g}/\text{filling}/\text{day}$ ). However, they noted that a REL is defined as a level of exposure that is free of anticipated health effects. As a result, the authors point out that health consequences of exceeding this REL for Hg through exposure to amalgam fillings or from other sources of exposure, cannot be determined simply by exceeding the REL-associated dose.

#### [Mercury in human hair as an indicator of the fish consumption.](#)

Kruzikova K, Modra H, Kensova R, Skocovska B, Wlasow T, Svoboda T, Svobodova Z. Neuro Endocrinol Lett. 2008 Oct;29(5):675-9.

The primary objective of this study was to assess whether or not fish consumption correlated with mercury levels in hair. The number of amalgam fillings was also documented. Health effects were not evaluated. A total of 174 hair samples from children 9-17 years old were analyzed. The authors concluded that the level of mercury in hair correlated with fish consumption, but did not correlate with age, gender or the number of amalgam fillings.