### Title

Dental Amalgam Fillings: An Under-Investigated Source of Mercury Exposure☆




### ISBN

9780444639516



### Author

Bates, Michael N



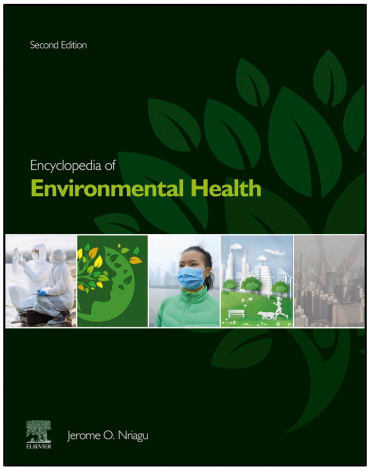
### Publication Date

2019

### DOI

10.1016/b978-0-12-409548-9.11230-8

Peer reviewed






From Bates, M.N., 2019. Dental Amalgam Fillings: An Under-Investigated Source of Mercury Exposure. In: Nriagu, J. (Ed.), Encyclopedia of Environmental Health. Elsevier, vol. 2, pp. 25–36. https://dx.doi.org/10.1016/B978-0-12-409548-9.11230-8
ISBN: 9780444639516

# Dental Amalgam Fillings: An Under-Investigated Source of Mercury Exposure☆

**Michael N Bates,** University of California, Berkeley, CA, United States



## Abbreviations

**μg/gC** Microgram per gram of creatinine
**μg/m$^3$** Microgram per cubic meter
**μg/L** Microgram per liter
**95% CI** 95% confidence interval
**γ-GT** Gamma glutamyltranspeptidase
**CFS** Chronic fatigue syndrome
**ICD-9** International Classification of Disease, Version 9
**IgE** Immunoglobulin type E
**LBW** Low birth weight
**MS** Multiple sclerosis
**NAG** *N*-acetyl-β-glucosaminidase
**NECAT** New England Children's Amalgam Trial
**OR** Odds ratio

## Introduction

It has been known since ancient times that mercury metal combines with other metals to form solid amalgams. The Chinese, during the Tang Dynasty in the 7th century AD, may have been the first to employ amalgam compositions for restoration of decayed tooth structure and function. Modern use of amalgam restorations in dentistry dates to about 1818 when they were reinvented by Louis Regnart, a Paris physician. Before amalgams, tooth fillings were made from various materials, including gold foil and molten metal mixtures. The former was expensive and the latter painful. Amalgam use in dentistry has been controversial since around the 1830s, in part because it threatened the profitable use of gold as a filling material, but also because of health concerns about mercury. Dental amalgam was introduced to the United States in 1833 by the Crawcour Brothers, who called it "Royal Mineral Succedaneum" (meaning "gold substitute"). The brothers made a lot of money in a short time by appealing to wealthier patients, but their dubious methods led to an increase in the level of opposition to amalgam.

The controversy has revived over the last 40 years or so, since analytical chemistry techniques became sensitive enough to show continuous release of mercury from dental amalgams. Some of this mercury is absorbed into the body and studies have repeatedly confirmed that amalgams constitute the main source of inorganic mercury exposure in nonoccupationally exposed populations.

Experts groups established by various international and regulatory agencies have considered the evidence for whether amalgam restorations may cause health damage. These groups have usually concluded that there was no evidence of harmful effects and, therefore, no basis for recommending against the continuing use of amalgams. However, in 2006, the Dental Products Panel, an advisory committee of the FDA, concluded that the available evidence on dental amalgams "neither supports nor refutes adverse health effects." In response, in July 2009, the FDA classified dental amalgam as a Class II (moderate risk) medical device and imposed several labeling requirements for amalgam products. At the same time, the agency concluded that "exposures to mercury vapor from dental amalgam do not put individuals age six and older at risk for mercury-associated adverse health effects." This remains the agency's position.

Amalgams fillings presently contain about 50% mercury, with the remainder mainly silver, with small amounts of copper, tin, or zinc. Although alternative filling materials are increasingly available, amalgam remains popular because of its comparative cheapness, durability, ease of use, and because it is less affected by moisture than other materials.

In 2013, the Minamata Convention on Mercury, intended to reduce exposures to and emissions of mercury and its compounds, was signed by representatives of the majority of countries in the world. It contains special provisions for dental amalgams,

☆ *Change History*: April 2018. Michael N. Bates updated the text. The title has changed by insertion of the word "under-investigated." The introduction has had mention of the Minamata Convention added. Sections on Parkinson's and Alzheimer's diseases have been updated to reflect new studies. A new section on auditory system effects has been added. Conclusions have been updated to reflect views of an expert committee of the European Union. Other than that, minor wording improvements have been made throughout and more references have been added.
This is an update of M.N. Bates, Dental Amalgam Fillings: A Source of Mercury Exposure, In Encyclopedia of Environmental Health, edited by J.O. Nriagu, Elsevier, 2011, Pages 11–20.



Encyclopedia of Environmental Health, Second Edition, 2019, 25–36

consisting of nine measures that countries make take, depending on their circumstances. These include national objectives for dental caries prevention and promoting the use of cost-effective and clinically effective alternatives for tooth restoration. Each ratifier of the convention is required to implement at least two of the measures.

Although there is general consensus that the use of dental amalgams is decreasing across the world, they remain the most frequently used filling material in posterior teeth, particularly in low and middle income countries. Before the advent of the Minamata Convention, a few, mainly Scandinavian, countries banned the use of amalgam fillings, particularly because of concerns about the potential for environmental mercury pollution. It has been estimated that, annually, about 7000 kg of amalgam-related mercury were released from crematoria worldwide, constituting about 0.8% of anthropogenic mercury emissions to the environment.

Apart from health concerns associated with release of mercury from amalgams, other disadvantages are esthetic, because of the color of the fillings, and, because has amalgam has no natural adherence to teeth, more healthy tooth must be removed to provide a mechanical foothold for the amalgam filling. Restorations made of composite resin and ionomer cement materials are much closer to tooth coloring and bond adhesively to healthy dentin. However, these alternatives are generally not as robust as amalgam fillings and require more frequent replacement, although materials are continually improving. The alternative materials are also usually considerably more expensive than amalgam restorations. **Table 1** provides a comparison of key characteristics for amalgam fillings and their main alternative–composite resin fillings.

That there is mercury exposure from amalgam fillings is no longer at issue. The question is whether this exposure causes harm to health. A scientifically-based answer to this question is important. If health effects do occur, then many hundreds of millions of people may be affected. Without overdoing the analogy, the experience with adding lead to gasoline, long thought to be of no toxicological consequence, teaches us the importance of carefully examining low-level population exposures to toxic metals. On the other hand, if amalgam fillings are safe, then unnecessary restrictions on their use could have major economic and public health consequences. If amalgam restorations were banned, then dental treatment would likely become prohibitively expensive for some or many people.

Effects of inorganic mercury on the nervous and renal systems are long established. However, mercury may also affect the immune, cardiovascular, respiratory, hematologic, gastrointestinal, and reproductive systems. Binding of mercury to the sulfhydryl groups of enzymes may be the mediator of many of these effects. Most information about the health effects of inorganic mercury exposure has come from studies of occupationally exposed populations. This information is relevant to assessment of the potential for amalgam fillings to cause health damage, but because the population of people with amalgam restorations contains younger, older, and possibly more susceptible people than occupationally exposed populations, and because exposure to amalgam restorations can be over a much longer time period, it is important that the safety of amalgams be confirmed with population-based epidemiologic studies.

This article considers the evidence for the safety of dental amalgam fillings and draws on studies of other inorganic mercury-exposed groups insofar as they may contribute usefully to the discussion. Exposures to organic mercury compounds (e.g., from fish or vaccine preservatives) are not considered, as the nature of their toxicity is quite different from that of inorganic mercury.

The signs and symptoms of inorganic mercury toxicity, sometimes referred to as "mercurialism," are well-established. Depending on the exposure, these include erethism (psychotic symptoms, including excessive timidity, anxiety, a desire to remain unobserved and unobtrusive, a pathological fear of ridicule with an explosive loss of temper when criticized), intention tremor, stomatitis, gingivitis, and excessive salivation. These manifestations of mercury toxicity are not discussed in this article, as the levels of mercury exposure from amalgam restorations are generally considered insufficient to cause them. The emphasis here is on (i) possible effects of mercury for which there has been more uncertainty, such as cardiovascular disease, neurodegenerative diseases, reproductive effects and effects in children; and (ii) toxic effects of mercury known to occur, but for which there is debate about whether they are caused by the levels of mercury exposure to which amalgam restorations may give rise (e.g., kidney effects).

**Table 1** Comparison of Amalgam fillings and composite fillings

| *Amalgam* | *Composites* |
|---|---|
| Easy to use (by dentists) | Requires higher skill level |
| Some bacteriostatic properties | Not bacteriostatic |
| Durable | Generally less durable, although improving |
| Highly resistant to wear | Less resistant to wear |
| Tolerant to moisture | Not moisture tolerant |
| Relatively inexpensive | Appreciably more expensive |
| Not esthetic in appearance | Esthetic appearance |
| Requires more removal of healthy tooth tissue to provide mechanical grip | Only removal of decayed tissue |
| Incomplete data on toxic hazards | Incomplete data on toxic hazards |
| Environmental mercury pollution (waste amalgam and cremation) a concern | Pollution not of concern |

## Mercury Uptake From Dental Amalgam

Amalgam fillings continuously release low levels of mercury vapor. Most is as $Hg^0$, which may be inhaled. Some mercury will be oxidized to $Hg^{2+}$ in the saliva and may be swallowed with small mercury particles from tooth abrasion caused by chewing and bruxism. There is some evidence that some of the released mercury may be transformed to methylmercury by bacteria in the oral cavity. The release rate of inorganic mercury will be determined by factors such as restoration size, the tooth and tooth surface on which it is placed, chewing habits, food type and texture, tooth grinding and brushing, and the surface area, chemical composition, and time since placement of the restoration. Inorganic mercury is absorbed from the gastrointestinal tract at a rate of no $>10\%$. About 80% of mercury vapor reaching the lungs is absorbed. Any methylmercury generated by oral bacteria would be $>95\%$ absorbed.

Correlations have been demonstrated between the number of amalgams and expired breath and urinary mercury concentrations. In a population-based sample of 1626 U.S. women, aged 16–49, recruited by the 1999–2000 National Health and Nutrition Examination Survey, it was estimated that for every 10 dental amalgam-filled tooth surfaces an increase in urinary mercury of about 1.8 μg per gram of creatinine (μg/gC) would occur (**Dye et al., 2005**). From a study of 550 nonoccupationally exposed adults, **Fig. 1** shows a monotonic increase in urinary mercury levels in relation to number of amalgam fillings. It also shows that there is a strong relationship with the number of occlusal (top surface) amalgam fillings (**Factor-Litvak et al., 2003**).

People with amalgam fillings who chew gum regularly, particularly those who use nicotine-containing gum as a smoking cessation aid, may be the most highly exposed. Urinary mercury levels in nicotine gum users have been shown to be in the range 2.8–14 nmol/nmol creatinine, which approaches the biological exposure index for mercury in urine of 20 nmol/nmol creatinine (35 μg/gC) set by the American Conference of Governmental Industrial Hygienists as an acceptable limit for occupational exposures.

Subjects with amalgam fillings tend to have higher concentrations of mercury in saliva and feces and the number of amalgam surfaces has been shown to be correlated with the mercury content of several tissues, including the kidney and brain at autopsy.

Signs and symptoms of mercury toxicity in occupational studies have usually occurred in association with mercury concentrations in air of $>50$ μg/m$^3$. These correspond to urinary mercury concentrations of $>100$ μg/L. Urinary mercury concentrations in people who have had no occupational mercury exposure may be as high as 20 μg/L.

For people without occupational exposure to mercury, daily absorption of mercury from ambient air is around 0.24 μg, compared to 3–17 μg from amalgam restorations. It has been estimated that in the Australian context, mercury derived from dental amalgams constitutes about 25%–50% of total body burden of mercury.

The change in mercury content of body fluids (blood, serum and urine) after removal of amalgam fillings has been investigated. In one study, 12 subjects were followed for up to 3 years after their amalgam fillings were removed using high-speed water-spray cutting and a vacuum extractor, but no rubber dam. After a transient initial increase in mercury content of blood and plasma, the serum mercury concentrations in these fluids and urine continued to decrease, according to a bi-exponential model, for the remaining period of follow-up, approaching concentrations found in people who had had no amalgam fillings placed.

Other studies have found an initial transient increase in urinary excretion of mercury after amalgam removal. This has been followed to a decline in urinary mercury levels to around 25% of their preremoval levels, after 1 year.

## Chronic Disease Incidence and Mortality

During 1968–69, 1462 Swedish women, aged 38–60, received medical and dental examinations at recruitment into a prospective cohort study. In the data analysis, the number of amalgam fillings at recruitment was investigated in relationship to episodes of myocardial infarction, stroke, diabetes, or cancer, and to overall mortality occurring over a 20-year follow-up period. Women

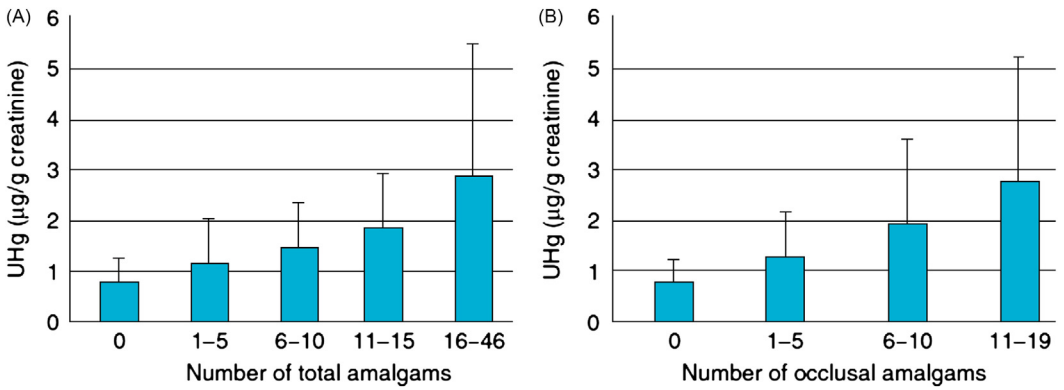



**Fig. 1** Relationships between UHg (μg/g creatinine) and (A) the number of total mercury-containing amalgam surfaces, and (B) the number of occlusal mercury-containing amalgam surfaces. Error bars represent 1 SD above the mean. *Source:* Factor-Litvak, P., Hasselgren, G., Jacobs, D., et al. (2003). Mercury derived from dental amalgams and neuropsychologic function. *Environmental Health Perspectives* **111**, 719–723.

with 20 or more amalgam-filled surfaces ($n = 632$) were compared with dentate women having 0–4 amalgam fillings ($n = 180$). Having a larger number of amalgam-filled surfaces was associated with lower risks for myocardial infarction, stroke, diabetes, and overall mortality (Ahlqwist et al., 1993).

Blood samples were collected at recruitment and analyzed for mercury content. The serum mercury concentrations were correlated with the number of amalgam restorations then present ($r = 0.84$, $P < 0.0001$). General mortality, myocardial infarction, stroke, diabetes, and cancer were assessed after 24 years of follow-up (Ahlqwist et al., 1999). No health outcome was associated with serum mercury concentration, but, after adjusting for age and education, there was a negative correlation with mortality rate ($P = 0.05$).

Since it is not likely that amalgams have a directly protective effect, this result is probably a result of confounding by access to dental treatment. In other words, healthier people may have better dental treatment access and receive more amalgam restorations.

The one other epidemiologic study with a large number of subjects that examined a broad range of health outcomes in relation to dental amalgam exposure is a retrospective cohort study of New Zealand military personnel (Bates et al., 2004). Within the New Zealand Defense Force dental treatment has been compulsory, regular, and without regard to rank. Longitudinal, tooth surface-specific dental treatment records for the study's 20-year follow-up period were available. These permitted construction of a time-varying exposure index expressed as amalgam surface-years. The cohort of 20,000 people was linked with national mortality, hospital discharge and cancer incidence records for the period 1977–1997. There were no associations between the amalgam exposure index and broad disease outcome categories. Nor were any associations identified between the exposure index and any specific causes of death or cancers. However, at the end of follow-up the cohort was still quite young and there had been few deaths ($n = 189$) or cancers ($n = 264$). Results for some of the more specific outcomes are summarized separately below.

## Neurologic Disease

Given that inorganic mercury is well-established as affecting the nervous system, it is perhaps not surprising that much concern has focused on possible associations between dental amalgam restorations and nervous system diseases, particularly diseases for which the etiology is still largely unclear–multiple sclerosis, Parkinson's disease, and Alzheimer's disease. There have also been concerns about possible neuropsychological and neurophysiological effects of mercury release from dental amalgam fillings.

### Multiple Sclerosis

The fact that both multiple sclerosis (MS) and dental caries prevalences tend to increase with increasing distance from the equator prompted suggestions of a common etiology. Later, it was hypothesized that this association may really be an association of MS with dental amalgam restorations, more prevalent in high caries areas. Since then there have been several studies investigating this possibility.

In one study a symptom questionnaire was administered to 42 MS patients whose amalgam restorations had been removed and 44 MS patients who retained their restorations (Siblerud and Kienholz, 1994). The group that still had their amalgams reported an average of 34% more MS-related symptoms within the last year than the amalgam removal group. The findings are difficult to interpret because of a difference in the method by which the two participant groups were recruited. Subjects retaining their amalgams were recruited in part through advertisements. This approach may have tended to attract people with more severe MS symptoms. Also, MS diagnoses were apparently not verified and there could have been a placebo effect from the amalgam removal.

Three epidemiologic case-control studies have investigated whether there is an association between MS and dental amalgams. A study in Canada recruited 143 incident MS cases and 128 age- and sex-matched controls (Bangsi et al., 1998). Dental histories were obtained from personal dentists. In the cases and controls, average numbers of amalgam fillings were 9.4 and 8.8, respectively ($P > 0.05$). Exposure-response relationships, based on a count of amalgam restorations and, separately, on time since placement of the first amalgam filling, provided weak evidence of increasing risk.

The second case-control study involved 39 English female MS cases, aged 25–65 at diagnosis (McGrother et al., 1999). Cases were diagnosed during 1977–85, but the study was conducted in 1989–90. Sixty-two age-matched controls were obtained from the same physician patient lists as the cases. During the study, all subjects received a full dental examination. Cases and controls had average numbers of 8.9 and 9.7, amalgam-filled teeth ($P = 0.40$). Prevalent cases of MS, some of whom had all their amalgam fillings removed after diagnosis, were used in this study. Also, compared to the controls, cases had often neglected their dental treatment. These features, consequential on using prevalent rather than incident cases, would probably have obscured any actual relationship between MS and amalgam restorations.

The third case-control study, from Italy, used 132 MS cases diagnosed in the last 16 years and 423 controls matched on sex, age, and residential area (Casetta et al., 2001). Information on amalgam restorations was obtained by questionnaire, from the study subjects themselves. Cases reported larger numbers of dental fillings than controls ($P < 0.05$). In those study subjects for whom the duration since first amalgam placement was $>5$ years, there was a weakly increasing trend in the odds ratios associated with the number of amalgam fillings. Limitations of this study included use of prevalent cases and the method of obtaining amalgam restoration data. Individuals are unlikely to accurately recall when and how many amalgam restorations they have had. Such recall is very likely to be subject to bias, particularly if some MS patients believed their condition was caused by their amalgams.

Finally, the previously mentioned cohort study of New Zealand military personnel obtained a relative risk estimate of 1.24 (95% CI: 0.99–1.53, $P = 0.06$) for a cumulative exposure unit of 100 amalgam-filled surface-years. For a person with the average cumulative exposure in the cohort of 628 amalgam-filled surface-years, this equates to a relative risk estimate of 3.9, compared to someone who has had no amalgam fillings.

Overall, the available studies are few, none are recent, and together they are inconclusive. Study limitations include small numbers of study subjects or MS cases, use of prevalent cases lack of confirmation of case diagnoses, and inadequate amalgam exposure data.

### Parkinson's Disease

A classic symptom of mercury poisoning, as it is for Parkinson's disease, is fine tremor of the hands. This is, at least in part, one reason why mercury has been suspect in Parkinson's etiology. However, the tremor frequency associated with mercury exposure is higher than found with Parkinson's disease. Nonetheless, it has long been suggested that dental amalgams might be a cause of Parkinson's disease, for which there are no confirmed environmental causes, although some pesticides are suspected.

Two epidemiology study have investigated whether dental amalgams are associated with Parkinson's disease. The first, a German case-control study compared 380 prevalent Parkinson's disease patients with 379 neighborhood controls and 376 regional controls (**Seidler et al., 1996**). At the interview, cases were asked how many amalgam fillings they had before Parkinson's disease onset; controls were asked how many amalgam fillings they had 1 year before interview. On average, study cases reported more amalgam fillings ($n = 7.8$) than either neighborhood controls ($n = 6.5$, $P = 0.0008$) or regional controls ($n = 6.1$, $P < 0.00005$). Using the regional controls and after adjustment for the number of remaining teeth, odds ratios for increasing exposure in quartiles of amalgam fillings per remaining number of teeth, relative to the low exposure quartile, were 1.7 (95% CI: 1.0–2.7), 2.5 (1.4–2.5), and 1.9 (1.1–3.3) ($P$ for trend = 0.003). The use of prevalent Parkinson's cases and amalgam exposures based on self-report at interview were major limitations of this study. Dental records or dental examinations were not used.

Most recently, a retrospective cohort study of the association between Parkinson's disease and dental amalgams was carried out using the Taiwanese National Health Insurance Research database, which contains dental amalgam placement data since 2000 (**Hsu et al., 2016**). 10,236 persons with amalgam fillings during the period of follow-up (2002–08) were individually age- and sex-matched with 10,236 persons who did not receive such fillings. Incidence rates of Parkinson's disease diagnosis across the follow-up period were compared between the two groups. Incidence rates in the two groups were 2.35 and 1.04 cases per 1000 person-years of follow-up for the amalgam and non-amalgam groups, respectively. The adjusted hazard ratio (HR) was 1.58 (95% CI: 1.12, 2.23). Co-variate adjustment was carried out only for co-morbidities, particularly diabetes, hypertension, hyperlipidemia and cardiovascular disease. Notable about this study was the high rate of all these co-morbidities in the amalgam group compared to the non-amalgam group. There are at least two conceivable explanations for this: either amalgam fillings are a cause of the differences in co-morbidities between the two groups or people receiving amalgam fillings are substantially different in terms of their health or socio-economic statuses from people not receiving amalgam fillings. Based on present knowledge, the latter explanation seems more likely. The other consideration is that the study was unable to take into account amalgam fillings before about 2000, although the overall impact of such exposure misclassification is likely to have been nondifferential and attenuated the hazard ratios. So that in itself would be unlikely to explain the elevated HR obtained.

In conclusion, the evidence for an association of dental amalgam fillings and Parkinson's disease is very limited, although databases such as the one used in Taiwan offer a potentially valuable and cost-effective means of investigating this association.

### Alzheimer's Disease

Although there have long been claims that dental amalgam fillings may be a cause of Alzheimer's disease there has been little effort to investigate this hypothesis. An Alzheimer's disease case-control study investigated whether there was an association with dental amalgam exposure (**Saxe et al., 1999**). The study included 68 Alzheimer's cases at autopsy and 33 controls obtained from a volunteer brain donation program. Dental histories were available from dental records and X-rays for both cases and controls. Mercury analyses were carried out for samples from the brain cerebral cortexes. Three amalgam exposure indexes, based on "event" (amalgam placement, repair or removal) and location and after placement, were used. No associations were found between any of the exposure indices and either Alzheimer's disease or mercury concentrations in the brain. Although this study had high quality dental history data, the number of subjects was small.

An ecological study of people in five Canadian regions obtained a correlation between prevalences of Alzheimer's disease and edentulism (**Lund et al., 2003**). This was interpreted by the authors as arguing against any association between amalgam restorations (in people with teeth) and Alzheimer's disease. However, it could be argued that the reverse is the case—since prevalence of edentulism is an indicator of higher caries rates, the edentulous group might have had a higher past exposure to amalgams.

In an Australian study that examined occupational risk factors for Alzheimer's disease, a panel of occupational hygienists evaluated job details for 170 Alzheimer's disease cases and 170 age- and sex-matched controls (**Gun et al., 1997**). An odds ratio of 1.78 (95% CI 0.44–2.85) was obtained for occupational exposure to mercury. However, only 4.1% of the cases and 2.4% of the controls had had mercury exposure.

Most recently a study took advantage of the Taiwanese Longitudinal Health Insurance Database, which contains health data, including recording of dental amalgam fillings placed since 2001 (**Sun et al., 2015**). The study included a total of 207,657

beneficiaries aged 65-years and older in 2010. For placement of any amalgam fillings in the period 2001–10, the ORs for association with Alzheimer's disease were 1.07 (95% CI: 0.96–1.20) for men and 1.13 (1.02–1.25) for women. Although suggestive of an association, co-variate adjustment was carried out only for age, income, and Region of Taiwan. Small measures of effect, such as those obtained in this study, could easily be influenced by unmeasured confounding factors or other bias. Nonetheless, databases such as was used in this study offer excellent opportunities for exploring such associations, particularly if a wider range of covariates is available.

Overall, the available studies provide only limited evidence for a role of dental amalgams or mercury in Alzheimer's disease etiology.

### Neuropsychological and Neurophysiological Function

There have been a number of studies that investigated whether amalgams were associated with neuropsychological or neurophysiological functioning. A study of 129 nuns, aged 75–102, living in a retirement home used an intraoral camera to assess coexisting amalgam placements (Saxe et al., 1995). Results of eight cognitive function tests completed by the nuns provided no evidence of deterioration of performance that was correlated with amalgam restorations. Although this study had good data on existing amalgam restorations, it lacked information on duration of placements.

A study using 587 participants drawn from the Swedish Twin Registry, obtained self-rated health assessments and the results of tests of personality and memory function (Bjorkman et al., 1996). Dental status was obtained by oral examination. Suggestions that a higher number of amalgam surfaces was associated with better health mostly disappeared after adjusting for age, sex, education, number of teeth, and smoking behavior. The lack of information on duration of amalgam filling placement would have weakened any true causal associations that were present.

A well-conducted study of 550 residents of New York, aged 30–49 years, obtained a correlation between urinary mercury excretion and both the total number of amalgam-filled surfaces and the number of amalgam-filled occlusal surfaces (Factor-Litvak et al., 2003). No associations were found between scores on neuropsychological tests and either urinary mercury concentrations or numbers of amalgam restorations. This study also did not have information on duration since placement of fillings.

There have been few studies of whether amalgam restorations are associated with reductions in peripheral nerve function. However, neurologic examinations (not including nerve conduction testing) and quantitative sensory testing were carried out on 2038 U.S. military personnel (Kingman et al., 2005). Amalgam exposure (total number of filled surfaces) was assessed by oral examination. No associations were found between amalgam exposure and either clinical neuropathy signs or sensory thresholds. Again, a study limitation (acknowledged by the authors) was the unavailability of longitudinal amalgam placement and removal data.

Two clinical trials, described in more detail below, in both of which children were randomly allocated to one of two treatment groups, receiving either amalgam or resin composite fillings, found no evidence for deleterious effects on neuropsychological development associated with amalgams. One of these studies, the New England Children's Amalgam Trial (NECAT), followed 534 children for 5 years, beginning at ages 6–10 (Bellinger et al., 2006). The Casa Pia study followed 507 children aged 8–10 in Lisbon, Portugal, for 7 years (DeRouen et al., 2006). The latter study also carried out nerve conduction tests and found no difference between the two groups.

In summary, the studies provide no support for an effect of amalgam restorations on neurologic function.

### Auditory System Effects

A British study, prompted by knowledge of mercury ototoxicity, investigated whether dental amalgam fillings were associated with hearing loss (Rothwell and Boyd, 2008). It recruited 39 non-smoking women, aged 40–45, with no history of hearing or ear problems. Their fillings were counted by a dentist and their hearing thresholds were measured using pure-tone air-conduction audiometry. Increasing numbers of amalgams were associated with poorer hearing thresholds, measured in decibels (dB), between frequencies of 8 and 16 kHz, and possibly as low as 4 kHz. The strongest association, at 14 kHz, shows a clear trend of increasing hearing threshold (i.e., poorer hearing) with number of amalgam fillings at time of examination ($R2 = 0.35$, $P < 0.001$). This was equivalent to a worsening of hearing threshold for each amalgam by 2.4 dB (95% confidence interval: 1.3, 3.5 dB). No other published study has attempted to confirm these results.

## Effects on Immunologic Function

Animal experiment have generated autoimmune responses to low inorganic mercury doses, particularly an increase in immunoglobulin type E (IgE).

A Swedish study found a statistically significant correlation between immunoglobulin type A (IgA) and plasma mercury concentration, but no correlation of plasma mercury with IgE in 15-year olds (Herrstrom and Hogstedt, 1994). A follow-up study in 19-year old students ($n = 77$), half with allergic diseases (asthma, allergic rhinitis, eczema), provided no confirmation of the correlation between IgA and plasma mercury concentration (Herrstrom et al., 1997). There was also no association of plasma mercury concentration with IgE or with allergic disease, but a correlation with $IgG_2$ was found ($r = 0.33$, $P = 0.003$).

No associations were found with numbers of amalgam restorations, when 33 children with Henloch-Schönlein purpura and another 31 with acute glomerulonephritis, both autoimmune diseases, when these children were compared with a matched control group (Herrstrom et al., 1996).

So far, the only detrimental health effect unequivocally associated with dental amalgams is allergic reactions in the mouth. These are very rare and usually improve after removal of the amalgam restorations.

## Effects on Kidney Function

It is well established that the kidney is one of the primary target organs of inorganic mercury exposure, particularly at higher doses. Most known examples involve occupational exposures or ingestion of mercury in traditional medicines or teething powders. Manifestations can range from increased urinary excretion of certain proteins, such as *N*-acetyl-β-glucosaminidase (NAG), transferrin or β2-microglobulin, the nephrotic syndrome (edema and albuminuria) and acute renal failure.

Concerns about possible renal effects of dental amalgam mercury release were prompted by a study showing reduced inulin clearance by the kidneys and changes in urinary electrolyte patterns in six sheep, each given 12 occlusal fillings (Boyd et al., 1991), although this study has been criticized as involving an unrealistic exposure scenario.

That people with amalgam restorations have higher kidney mercury concentrations than people without amalgams has been confirmed in several studies (Nylander et al., 1987, Barregard et al., 1999). Other studies have investigated renal function in relation to amalgam loading. A study of 48 healthy male students, aged 17–22 years, found no association between urinary proteins indicative of kidney damage and either number of dental amalgam restorations or urinary mercury levels (Herrstrom et al., 1995).

Another study involving 100 healthy adults, 18–44 years, detected a small increase in urinary NAG levels in people with amalgam fillings, but the authors considered it to have probably no clinical significance (Eti et al., 1995).

Renal function changes after removal of an average of 18 amalgam fillings from 10 healthy volunteers were investigated (Sandborgh-Englund et al., 1996). Significantly lower mercury levels were present in urine 60 days after the amalgam removal, but there was no change in renal function indicators.

A retrospective cohort study of 20,000 New Zealand military personnel found no associations between an index of longitudinal dental amalgam exposure and any of a number of kidney diseases found in hospital discharge data (Bates et al., 2004).

Finally, two randomized trials in children, described in more detail below, measured kidney function in a group with amalgam filling placements with a group that received composite resin fillings. Measures of glomerular and tubular kidney function measured in the NECAT were urinary albumin, alpha-1-microglobulin, γ-glutamyl transpeptidase (γ-GT) and NAG (Barregard et al., 2008). The only difference in the markers between the two groups was that, relative to children in the composite group, children in the amalgam group had an elevated prevalence of microalbuminuria (defined as urinary albumin $>30$ mg/g creatinine) in years 3 and 5 of the 5 years of follow-up (adjusted OR $= 1.8$, 95% CI: 1.1–2.9). However, there was no significant increase in the microalbuminuria associated with either the number of amalgam fillings ($P = 0.30$) or urinary mercury excretion levels ($P = 0.71$).

Also of note in the NECAT study was the absence of any association of amalgam treatment with NAG. A study of children living around nonferrous metal smelters in several European countries found increased levels of NAG associated with urinary mercury levels lower than those found in the NECAT children (de Burbure et al., 2006). However, it is possible that the results of the European study reflect uncontrolled confounding or interactions with other exposures, particularly metals.

The other randomized trial, the Portugal-based Casa Pia study, measured urinary albumin and γ-GT in the children in the study (Woods et al., 2008). This study found no differences between the treatment groups over the course of the 7-year follow-up, including no difference in the prevalence of microalbuminuria.

The difference between the two randomized children's trials in results for microalbuminuria is not readily explained by differences in exposure, as children in the amalgam treatment group in NECAT had lower mean numbers of tooth surfaces restored with amalgam and surface-years of amalgam exposure (11.5 and 31.7, respectively) than the amalgam-treated children in the Casa Pia study (16.1 and 50.1, respectively). The authors of the NECAT study suggested that their albuminuria result might be attributable to chance (Barregard et al., 2008).

In summary, although studies are few, there is only very limited evidence that dental amalgam restorations may affect kidney function and the preponderance of evidence suggests that they probably do not.

## Studies of Self-Reported Symptoms

Various studies have investigated the relationship between dental amalgam restorations and self-reported symptoms. Broadly, these studies fall under two general study designs:

1. Investigations of symptoms before and after amalgam filling have been removed. These are often case-series, sometimes large, in which people have reported symptom relief after removal of their amalgam fillings, or studies in which symptom changes are compared in a group with and a group without amalgam removal. As well as symptom relief, diseases for which recovery has

been reported after amalgam removal include Parkinson's disease, Crohn's disease, MS, epilepsy, asthma, scleroderma, paranoia, and blindness.

2. Investigations of associations between symptom prevalence and measures of amalgam exposure, as estimated from dental histories or dental examinations at the time of the study. These studies may involve a comparison between a group of people who believe themselves harmed by their amalgam fillings and a group of people without such belief.

Of these two study designs, results of the first are very likely to be influenced by an uncontrolled placebo effect. Therefore, they contribute little to the debate and are not considered further here. Results of the second study design are less likely to be influenced by the placebo effect, although they still may be affected by other types of bias. Studies of this type are briefly reviewed here.

Self-perceived health was compared in 50 college students who had an average of 10 amalgam fillings with 51 students with no amalgam fillings (**Siblerud, 1989**). Subjects with amalgams reported being less happy, as well as more frequent suicidal tendencies. The amalgam group reported 61% more symptoms overall. This group also reported heavier consumption of sweets, alcohol, cigarettes and coffee than the nonamalgam group. Interpretation is difficult because results are potentially confounded by these differences. The amalgam subjects had a significantly higher average blood pressure than the non-amalgam group, as well as reporting a significantly greater frequency of heart or chest pains and tachycardia, and were more likely to suffer from tiredness, chronic fatigue, and anemia (**Siblerud, 1990**). In the data analysis there was no adjustment for the lifestyle factors.

Other studies have generally reported no associations between amalgam restorations and symptom prevalence. A study in Sweden of 1024 dentate women, aged 38–72, found no positive correlations between symptoms and the number of amalgam fillings, but a few symptoms were inversely correlated with amalgam numbers (**Ahlqwist et al., 1988**).

A Norwegian study compared 99 patients who self-referred with multiple symptoms, that they personally considered were caused by their amalgam fillings, to 272 other patients (**Malt et al., 1997**). No correlation was found between symptom prevalence and number of fillings. In another study, 50 Swedish patients who self-referred because of symptoms that they considered were caused by their dental amalgams were compared to a matched comparison group of 50 patients (**Bratel et al., 1997a,b**). Average numbers of amalgam surfaces in the two groups were much the same (28.2 and 29.0, respectively).

In a large German study that examined prevalence of 48 different symptoms in 4787 patients, aged 21–60, a greater number of amalgam-filled surfaces was associated with a lower prevalence of symptoms (**Melchart et al., 1998**). A similar result was found in a study of 587 individuals, aged 46–89 (mean: 66), drawn from the Swedish Twin Registry (**Bjorkman et al., 1996**).

Similar results were found in two other studies, each with about 40 patients who considered themselves harmed by amalgams and 40 referent subjects (**Bailer et al., 2001**, **Ganss et al., 2000**). Both studies found no differences between the compared groups in terms of numbers of amalgam fillings or blood or urinary mercury levels.

Chronic fatigue syndrome (CFS) (ICD-9 code 780) is a condition, involving symptoms, but usually no objective signs. There has been a widespread popular belief that CFS is associated with dental amalgams, but little epidemiological study of this hypothesis. A retrospective cohort study of New Zealand military personnel found no association between cumulative dental amalgam exposure and CFS (**Bates et al., 2004**). The relative risk estimate for CFS in relation to an exposure unit of 100 amalgam-filled surface-years was 0.98 (95% CI: 0.94–1.03).

In summary, the preponderance of evidence, particularly from larger studies, suggests amalgam restorations are not associated with subjective symptoms or chronic fatigue syndrome.

## Reproductive Effects

Generally, epidemiological studies have shown little or no effect of inorganic mercury on reproductive parameters, including fertility. In the cohort study of New Zealand military personnel described above there were 1062 births categorized as "complications of pregnancy and childbirth" (ICD-9 codes 630-677), but no association between these conditions and cumulative amalgam exposure.

Studies have investigated whether mothers' dental treatment during pregnancy affects the birth outcome. A case-control study in Washington State of 1117 low birth weight (LBW) infants and 4468 controls found no association of LBW with placement of dental amalgam fillings in the mothers during their pregnancies (**Hujoel et al., 2005**). Another study found no associations between placement or removal of dental amalgams in mothers' mouths during pregnancy with gestational age, birthweight, or the child's communicative ability at 15 months of age (**Daniels et al., 2007**). However, as acknowledged by the authors, collection of dental treatment by mailed questionnaire at 33 months postpartum is likely to be associated with nondifferential recall error that would bias any true associations towards the null.

Even though there is little evidence for reproductive effects induced by dental amalgams, there is evidence of in utero exposure: hair levels of mercury in fetuses have been shown to be correlated with the number of amalgam fillings that their mothers have.

## Effects in Children

Until relatively recently there had been relatively few epidemiological studies of health effects of amalgam fillings in children and no health effects had been associated with either mothers' amalgam fillings (in utero or breast milk transfer) or amalgam fillings in

older children. The results of two randomized trials in children have been published. The first of these, the New England Children's Amalgam Trial (NECAT), conducted between 1997 and 2005, involved 534 children who, at baseline, were aged 6–10 years, had no previous amalgam fillings, and had at least two posterior teeth with caries (**Bellinger et al., 2006**). These children were randomized to two groups—dental amalgam or resin composite fillings. The children were followed for 5 years, during which further fillings were placed while maintaining the treatment assignment. The study was sufficiently large to be able to detect a 3-point decline in IQ in one group relative to the other group over the course of the follow-up. Study results showed no evidence of adverse effects of amalgam in relation to IQ, neuropsychological function, psychiatric or behavioral symptoms, or kidney function (**Bellinger et al., 2006, 2007a,b**, **Barregard, 2008**).

The other study, known as the Casa Pia study, involved randomizing 507 children, aged 8–10, in Lisbon Portugal to amalgam and resin composite treatment groups. To be eligible for the study children needed to have at least one carious lesion on a permanent tooth and have had no previous amalgam fillings. Follow-up was for 7 years. No evidence of differences between the two groups was found for measures of memory, attention, visuo-motor function, nerve conduction or kidney function (**DeRouen et al., 2006**, **Woods et al., 2008**).

## Overview and Conclusions

Probably billions of people throughout the world have mercury amalgam fillings in their teeth. Although use of amalgam fillings has been decreasing, particularly in developed countries, it has been estimated that, between 1993 and 2008, about 900 million dental amalgam fillings were inserted in the United States—an average of 60 million per year.

Historically, people have been exposed to mercury from many sources, but there are now relatively few that are substantial. Dental amalgam has been characterized as one of "the three modern faces of mercury" (**Clarkson, 2002**). The other two "modern faces" are methyl mercury in fish and ethyl mercury (thimerosal), used as a preservative in vaccines. These three sources of exposure share the characteristics of being very widespread, they are all associated with some benefits, and for all of them there is some uncertainty or controversy about possible health effects.

Exposures to mercury from dental amalgams are clearly below mercury exposures shown to cause health effects in studies of people with occupational mercury exposure. However, studies of occupationally exposed populations commonly are affected by selection bias, often termed the "healthy worker effect," in which healthier people are selected into the workforce at the beginning of employment and those who are more refractory to the effects of work exposures remain employed in the industry. Also, in epidemiological studies of industrially exposed populations, durations of exposure and follow-up can be short, and occupational populations may be too small to detect uncommon health effects. People with amalgam restorations constitute a broader population spectrum and include more young, elderly and unwell people than are usually found in employed populations. Also, unless they have a very long period of follow-up, occupational studies are less likely to detect risk increases in diseases that mainly occur in the elderly (e.g., Alzheimer's or Parkinson's diseases) or nonmalignant diseases of low incidence (e.g., multiple sclerosis). Considering the very large number of people with dental amalgam fillings, even a quite small relative risk increase could have serious public health implications. A rare effect caused by mercury (in teething powders) was acrodynia, also known as pink disease, which it is estimated to have occurred in one exposed child in 500.

Despite 200 years of the modern period of use of dental amalgams and their ubiquitous prevalence, support for their continued use has historically been based on absence of evidence of harm, rather than demonstrations of actual safety. Characteristic of official statements is that by the US Food and Drug Administration, in 2002: "no valid scientific evidence has shown that amalgams cause harm to patients with dental restorations, except in the rare case of allergy." The American Dental Association has relied on such assessments.

Accepting that it is difficult to prove a negative, it is still appropriate to define types of harm that could potentially be caused by amalgam fillings and apply a systematic and critical evaluation method to available studies, particularly epidemiology studies, to clearly define those areas of concern that have been adequately investigated and those which require further study. A different approach to this evaluation, used by the FDA, is to rely on a comparison of estimated exposures to mercury from amalgam fillings against mercury exposure standards, as established by the US Environmental Protection Agency and the Agency for Toxic Substances and Disease Registry (ATSDR). A disadvantage of this approach is that the reference standards are unavoidably based on limited data and data obtained from small numbers of subjects. The subsequent numerical comparison of exposure versus standard does not explicitly address these limitations and can give a misleading impression of certainty.

Considering the extremely widespread and long-standing nature of the exposure and that it is the main source of inorganic mercury body burden in nonoccupationally exposed populations, there have been remarkably few analytic epidemiological investigations of possible health effects of dental amalgams. Studies that have been carried out have often had very small numbers of participants or other methodological limitations that make interpretation difficult or impossible. The chief limitation has been amalgam exposure assessment, which has usually been based on the number of dental amalgam fillings at time of the study and has not taken into account how long the amalgams have been in place or other aspects of dental treatment history, such as tooth loss. Most studies have involved some form of dental examination, but some studies have asked people to report their own amalgam history, an approach likely to lead to a high degree of misclassification, even of current amalgams.

A difficulty in obtaining longitudinal amalgam exposure data is that people change dentists over the course of their lifetimes, but their treatment records are often not transferred between dentists. Also, these records are not maintained by dentists in a consistent way, making difficult a comparison of amalgam placement histories across study participants. Another difficulty in study interpretation is confounding by access to dental treatment. People in higher socio-economic groups usually have better access to dental treatment. Because of this they may have more amalgam restorations. The same people are likely also to maintain better health. It is likely that this accounts for associations between amalgam exposure and better health found in several population-based studies. A cohort study of New Zealand military personnel went some way towards overcoming these limitations. These personnel received regular and consistent dental treatment, regardless of rank, and comprehensive longitudinal treatment records were available for the period of military service.

Two randomized trials in children have provided important and much-needed reassurance about possible impacts of amalgam placements in children. However, the cumulative exposure of the study participants was small in relation to lifetime exposure and longer-term follow-up would be necessary to provide greater confidence that there is not an eventual cumulative effect. Also, there may be genetically susceptible sub-populations that have yet to be discovered.

In summary, despite the longstanding use of dental amalgam for tooth restoration, epidemiologic data to establish its safety are less than ideal for such a widespread exposure. However, the data that are available are for the most part reassuring, particularly for kidney diseases, effects on neuropsychological function, chronic fatigue syndrome, nonspecific symptom complexes, and effects in children. A small study that appeared to show hearing loss associated with amalgam fillings deserves to be followed up. Apart from that, most in need of further study are neurodegenerative diseases, particularly MS, Parkinson's disease, and Alzheimer's disease, for which the current evidence is limited and, to the extent that it exists, is equivocal. This is consistent with the views of the FDA. In a statement accompanying the 2009 classification of dental amalgam as a Class II medical device, the FDA stated that there is "a paucity of studies" that evaluate a link between dental amalgam and neurological and neurodegenerative diseases, such as Parkinson's disease, Alzheimer's disease and MS. A 2015 review by an expert committee of the European Commission concluded that "current evidence does not preclude the use of… amalgam… in dental restorative treatment." However, it went on to say that "there is a need for further research, particularly relating to evaluation of the potential neurotoxicity of mercury from dental amalgam and the effect of genetic polymorphisms on mercury toxicity."

Finally, the fact that this article has focused on mercury amalgam fillings should not be taken to imply that the alternative filling materials are safe. There are many such alternative materials now available. Although clinical use over the last 40 years or so has revealed little in the way of harmful effects from these fillings (other than allergies), they have not been comprehensively studied.

***See also:*** Mercury Toxicity; Mercury in Air; Minamata Disease; Gold and Amalgams: Environmental Pollution and Health Effects.

## References

Ahlqwist, M., Bengtsson, C., Furunes, B., Hollender, L., Lapidus, L., 1988. Number of amalgam tooth fillings in relation to subjectively experienced symptoms in a study of Swedish women. Community Dentistry and Oral Epidemiology 16, 227–231.

Ahlqwist, M., Bengtsson, C., Lapidus, L., 1993. Number of amalgam fillings in relation to cardiovascular disease, diabetes, cancer and early death in Swedish women. Community Dentistry and Oral Epidemiology 21, 40–44.

Ahlqwist, M., Bengtsson, C., Lapidus, L., Gergdahl, I.A., Schutz, A., 1999. Serum mercury concentration in relation to survival, symptoms, and diseases: Results from the prospective population study of women in Gothenburg, Sweden. Acta Odontologica Scandinavica 57, 168–174.

Bailer, J., Rist, F., Rudolf, A., Staehle, H.J., Eickholz, P., Triebig, G., Bader, M., Pfeifer, U., 2001. Adverse health effects related to mercury exposure from dental amalgam fillings: Toxicological or psychological causes? Psychological Medicine 31, 255–263.

Bangsi, D., Ghadirian, P., Ducic, S., Morisset, R., Ciccocioppo, S., Mcmullen, E., Krewski, D., 1998. Dental amalgam and multiple sclerosis: A case-control study in Montreal, Canada. International Journal of Epidemiology 27, 667–671.

Barregard, L., 2008. Exposure to inorganic mercury: From dental amalgam to artisanal gold mining. Environmental Research 107, 4–5.

Barregard, L., Svalander, C., Schutz, A., Westberg, G., Sallsten, G., Blohme, I., Molne, J., Attman, P.O., Haglind, P., 1999. Cadmium, mercury, and lead in kidney cortex of the general Swedish population: A study of biopsies from living kidney donors. Environmental Health Perspectives 107, 867–871.

Barregard, L., Trachtenberg, F., Mckinlay, S., 2008. Renal effects of dental amalgam in children: The New England children's amalgam trial. Environmental Health Perspectives 116, 394–399.

Bates, M.N., Fawcett, J., Garrett, N., Cutress, T., Kjellstrom, T., 2004. Health effects of dental amalgam exposure: A retrospective cohort study. International Journal of Epidemiology 33, 894–902.

Bellinger, D.C., Trachtenberg, F., Barregard, L., Tavares, M., Cernichiari, E., Daniel, D., Mckinlay, S., 2006. Neuropsychological and renal effects of dental amalgam in children: A randomized clinical trial. JAMA 295, 1775–1783.

Bellinger, D.C., Daniel, D., Trachtenberg, F., Tavares, M., Mckinlay, S., 2007a. Dental amalgam restorations and children's neuropsychological function: The New England Children's amalgam trial. Environmental Health Perspectives 115, 440–446.

Bellinger, D.C., Trachtenberg, F., Daniel, D., Zhang, A., Tavares, M.A., Mckinlay, S., 2007b. A dose-effect analysis of children's exposure to dental amalgam and neuropsychological function: The New England Children's amalgam trial. Journal of the American Dental Association (1939) 138, 1210–1216.

Bjorkman, L., Pedersen, N.L., Lichtenstein, P., 1996. Physical and mental health related to dental amalgam fillings in Swedish twins. Community Dentistry and Oral Epidemiology 24, 260–267.

Boyd, N.D., Benediktsson, H., Vimy, M.J., Hooper, D.E., Lorscheider, F.L., 1991. Mercury from dental "silver" tooth fillings impairs sheep kidney function. The American Journal of Physiology 261, R1010–R1014.

Bratel, J., Haraldson, T., Meding, B., Yontchev, E., Ohman, S.C., Ottosson, J.O., 1997a. Potential side effects of dental amalgam restorations. (I). An oral and medical investigation. European Journal of Oral Sciences 105, 234–243.
Bratel, J., Haraldson, T., Ottosson, J.O., 1997b. Potential side effects of dental amalgam restorations. (II). No relation between mercury levels in the body and mental disorders. European Journal of Oral Sciences 105, 244–250.
Casetta, I., Invernizzi, M., Granieri, E., 2001. Multiple sclerosis and dental amalgam: Case-control study in Ferrara, Italy. Neuroepidemiology 20, 134–137.
Clarkson, T.W., 2002. The three modern faces of mercury. Environmental Health Perspectives 110 (Suppl 1), 11–23.
Daniels, J.L., Rowland, A.S., Longnecker, M.P., Crawford, P., Golding, J., 2007. Maternal dental history, child's birth outcome and early cognitive development. Paediatric and Perinatal Epidemiology 21, 448–457.
de Burbure, C., Buchet, J.P., Leroyer, A., Nisse, C., Haguenoer, J.M., Mutti, A., Smerhovsky, Z., Cikrt, M., Trzcinka-Ochocka, M., Razniewska, G., Jakubowski, M., Bernard, A., 2006. Renal and neurologic effects of cadmium, lead, mercury, and arsenic in children: Evidence of early effects and multiple interactions at environmental exposure levels. Environmental Health Perspectives 114, 584–590.
DeRouen, T.A., Martin, M.D., Leroux, B.G., Townes, B.D., Woods, J.S., Leitao, J., Castro-Caldas, A., Luis, H., Bernardo, M., Rosenbaum, G., Martins, I.P., 2006. Neurobehavioral effects of dental amalgam in children: A randomized clinical trial. JAMA 295, 1784–1792.
Dye, B.A., Schober, S.E., Dillon, C.F., Jones, R.L., Fryar, C., Mcdowell, M., Sinks, T.H., 2005. Urinary mercury concentrations associated with dental restorations in adult women aged 16–49 years: United States, 1999–2000. Occupational and Environmental Medicine 62, 368–375.
Eti, S., Weisman, R., Hoffman, R., Reidenberg, M.M., 1995. Slight renal effect of mercury from amalgam fillings. Pharmacology & Toxicology 76, 47–49.
Factor-Litvak, P., Hasselgren, G., Jacobs, D., Begg, M., Kline, J., Geier, J., Mervish, N., Schoenholtz, S., Graziano, J., 2003. Mercury derived from dental amalgams and neuropsychologic function. Environmental Health Perspectives 111, 719–723.
Ganss, C., Gottwald, B., Traenckner, I., Kupfer, J., Eis, D., Monch, J., Gieler, U., Klimek, J., 2000. Relation between mercury concentrations in saliva, blood, and urine in subjects with amalgam restorations. Clinical Oral Investigations 4, 206–211.
Gun, R.T., Korten, A.E., Jorm, A.F., Henderson, A.S., Broe, G.A., Creasey, H., Mccusker, E., Mylvaganam, A., 1997. Occupational risk factors for Alzheimer disease: A case-control study. Alzheimer Disease and Associated Disorders 11, 21–27.
Herrstrom, P., Hogstedt, B., 1994. Allergic diseases, dental health, and socioeconomic situation of Swedish teenagers. Allergy, dental health, and social situation. Scandinavian Journal of Primary Health Care 12, 57–61.
Herrstrom, P., Schutz, A., Raihle, G., Holthuis, N., Hogstedt, B., Rastam, L., 1995. Dental amalgam, low-dose exposure to mercury, and urinary proteins in young Swedish men. Archives of Environmental Health 50, 103–107.
Herrstrom, P., Hogstedt, B., Aronson, S., Holmen, A., Rastam, L., 1996. Acute glomerulonephritis, Henoch-Schonlein purpura and dental amalgam in Swedish children: A case-control study. Science of the Total Environment 191, 277–282.
Herrstrom, P., Hogstedt, B., Holthuis, N., Schutz, A., Rastam, L., 1997. Allergic disease, immunoglobulins, exposure to mercury and dental amalgam in Swedish adolescents. International Archives of Occupational and Environmental Health 69, 339–342.
Hsu, Y.C., Chang, C.W., Lee, H.L., Chuang, C.C., Chiu, H.C., Li, W.Y., Horng, J.T., Fu, E., 2016. Association between history of dental amalgam fillings and risk of Parkinson's disease: A population-based retrospective cohort study in Taiwan. PLoS One 11, e0166552.
Hujoel, P.P., Lydon-Rochelle, M., Bollen, A.M., Woods, J.S., Geurtsen, W., Del Aguila, M.A., 2005. Mercury exposure from dental filling placement during pregnancy and low birth weight risk. American Journal of Epidemiology 161, 734–740.
Kingman, A., Albers, J.W., Arezzo, J.C., Garabrant, D.H., Michalek, J.E., 2005. Amalgam exposure and neurological function. Neurotoxicology 26, 241–255.
Lund, J.P., Mojon, P., Pho, M., Feine, J.S., 2003. Alzheimer's disease and edentulism. Age and Ageing 32, 228–229.
Malt, U.F., Nerdrum, P., Oppedal, B., Gundersen, R., Holte, M., Lone, J., 1997. Physical and mental problems attributed to dental amalgam fillings: A descriptive study of 99 self-referred patients compared with 272 controls. Psychosomatic Medicine 59, 32–41.
McGrother, C.W., Dugmore, C., Phillips, M.J., Raymond, N.T., Garrick, P., Baird, W.O., 1999. Multiple sclerosis, dental caries and fillings: A case-control study. British Dental Journal 187, 261–264.
Melchart, D., Wuhr, E., Weidenhammer, W., Kremers, L., 1998. A multicenter survey of amalgam fillings and subjective complaints in non-selected patients in the dental practice. European Journal of Oral Sciences 106, 770–777.
Nylander, M., Friberg, L., Lind, B., 1987. Mercury concentrations in the human brain and kidneys in relation to exposure from dental amalgam fillings. Swedish Dental Journal 11, 179–187.
Rothwell, J.A., Boyd, P.J., 2008. Amalgam dental fillings and hearing loss. International Journal of Audiology 47, 770–776.
Sandborgh-Englund, G., Nygren, A.T., Ekstrand, J., Elinder, C.G., 1996. No evidence of renal toxicity from amalgam fillings. The American Journal of Physiology 271, R941–5.
Saxe, S.R., Snowdon, D.A., Wekstein, M.W., Henry, R.G., Grant, F.T., Donegan, S.J., Wekstein, D.R., 1995. Dental amalgam and cognitive function in older women: Findings from the Nun study. Journal of the American Dental Association (1939) 126, 1495–1501.
Saxe, S.R., Wekstein, M.W., Kryscio, R.J., Henry, R.G., Cornett, C.R., Snowdon, D.A., Grant, F.T., Schmitt, F.A., Donegan, S.J., Wekstein, D.R., Ehmann, W.D., Markesbery, W.R., 1999. Alzheimer's disease, dental amalgam and mercury. Journal of the American Dental Association (1939) 130, 191–199.
Seidler, A., Hellenbrand, W., Robra, B.P., Vieregge, P., Nischan, P., Joerg, J., Oertel, W.H., Ulm, G., Schneider, E., 1996. Possible environmental, occupational, and other etiologic factors for Parkinson's disease: A case-control study in Germany. Neurology 46, 1275–1284.
Siblerud, R.L., 1989. The relationship between mercury from dental amalgam and mental health. American Journal of Psychotherapy 43, 575–587.
Siblerud, R.L., 1990. The relationship between mercury from dental amalgam and the cardiovascular system. Science of the Total Environment 99, 23–35.
Siblerud, R.L., Kienholz, E., 1994. Evidence that mercury from silver dental fillings may be an etiological factor in multiple sclerosis. Science of the Total Environment 142, 191–205.
Sun, Y.H., Nfor, O.N., Huang, J.Y., Liaw, Y.P., 2015. Association between dental amalgam fillings and Alzheimer's disease: A population-based cross-sectional study in Taiwan. Alzheimer's Research & Therapy 7, 65.
Woods, J.S., Martin, M.D., Leroux, B.G., Derouen, T.A., Bernardo, M.F., Luis, H.S., Leitao, J.G., Kushleika, J.V., Rue, T.C., Korpak, A.M., 2008. Biomarkers of kidney integrity in children and adolescents with dental amalgam mercury exposure: Findings from the Casa Pia children's amalgam trial. Environmental Research 108, 393–399.

## Further Reading

Bjørklund, G., Dadar, M., Mutter, J., Aaseth, J., 2017. The toxicology of mercury: Current research and emerging trends. Environmental Research 59, 545–554.
Clarkson, T.W., Magos, L., 2006. The toxicology of mercury and its chemical compounds. Critical Reviews in Toxicology 36, 609–662.
Counter, S.A., Buchanan, L.H., 2004. Mercury exposure in children: A review. Toxicology and Applied Pharmacology 198, 209–230.
Department of Health and Human Services: Food and Drug Administration. CFR part 872 dental devices: Classification of dental amalgam, reclassification of dental mercury, designation of special controls for dental amalgam, mercury, and amalgam alloy; final rule. Federal Register Vol. 74, no. 148, Tuesday, 4, 2009.
Goldwater, L.J., 1972. Chapter 20, mercury in dentistry, in mercury: A history of quicksilver. York Press, Baltimore, MD.

Hyson, J.M., 2006. Amalgam: Its history and perils. Journal of the California Dental Association 34, 215–229.
SCENHIR (Scientific Committee on Emerging and Newly Identified Health Risks), Health & Consumer Protection Directorate-General, European Commission. (2015). The safety of dental amalgam and alternative dental restoration materials for patients and users.
Schuurs, A.H., 1999. Reproductive toxicity of occupational mercury. A review of the literature. Journal of Dentistry 27, 249–256.
Soler, J.I., Ellacuria, J., Triana, R., Guinea, E., Osborne, J.W., 2002. A history of dental amalgam. Journal of the History of Dentistry 50, 109–116.
World Health Organization, 2003. Elemental mercury and inorganic mercury compounds: Human Health aspects. Concise International Chemical Assessment Document 50. WHO, Geneva.

## Relevant Websites

American Dental Association. (2009)—http://www.ada.org/en/about-the-ada/ada-positions-policies-and-statements/statement-on-dental-amalgam—Statement on Dental Amalgam.
U.S. Food and Drug Administration, 2017—https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DentalProducts/DentalAmalgam/ucm171094.htm—U.S. Food and Drug Administration, Department of Health and Human Services. (2017). About Dental Amalgam Fillings.
Wikipedia, n.d.—http://en.wikipedia.org/wiki/Amalgam_(dentistry)—Wikipedia article on dental amalgam.