FDA U.S. FOOD & DRUG ADMINISTRATION

CENTER FOR DEVICES & RADIOLOGICAL HEALTH

Epidemiological Evidence on the Adverse Health Effects Reported in Relation to Mercury from Dental Amalgam:

Systematic Literature Review (2010-Present)

September 2019

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Executive Summary

Mercury (Hg) is a naturally-occurring substance with known toxicities. Most people have some exposure to elemental mercury (Hg^0) / inorganic mercury (Hg^{2+}) and/or organic methylmercury (MeHg) distributed throughout the environment. Elemental mercury vapors released from dental amalgam, a dental restorative material containing approximately 50% elemental mercury are a source of non-occupational exposure among patients as well as occupational exposure among dental personnel, especially in dental clinics with sub-optimal mercury handling practices, e.g., use of non-encapsulated amalgam, inadequate ventilation, lack of personal protective equipment, and improper recycling of amalgam waste. Mercury from dental amalgam can be released into the environment in various ways, such as from improper dental waste management practices and from crematoria, which along with other sources of inorganic mercury that contaminate air, land, and groundwater, can be biomagnified throughout the food chain as methylmercury.

To address public concerns resulting in the ongoing discussion on whether to ban, phase-out, or continue use of dental amalgam in the United States (US), FDA has continued to monitor and review published studies on the potential adverse health effects associated with exposure to dental amalgam mercury. Previous literature reviews conducted by FDA addressed assessment of amalgam-attributed health outcomes in the general population and vulnerable subpopulations, such as pregnant women and their developing fetuses, breastfed infants, and children under the age of six. As a result of these reviews, exposure to dental amalgam was shown to correlate with mercury levels in biofluids, primarily urine and blood; however, no conclusive evidence was found in relation to clinically-manifested adverse outcomes in the general population and listed subpopulations. In 2019, FDA conducted a more comprehensive literature review of the risks of dental amalgam to the general population that was not limited to specific adverse outcomes or subpopulations presumed at higher risk. The current review included clinical/ epidemiological evidence on adverse outcomes attributed to the elemental/inorganic form of mercury from dental amalgam as well as the biomedical evidence on the likelihood of transformation within the body of inorganic mercury to organic mercury and its possible consequences. As a subject related to the FDA's efforts to evaluate safety questions related to medical device materials including metals, the safety of mercury exposure from dental amalgam will be further addressed at an upcoming Advisory Committee meeting.

The currently available evidence derived from studies from the US and other developed countries and based on the actual mercury measurements in large study populations reveals possible mercury increases in biofluids due to either occupational (dental professionals) or non-occupational exposure to dental amalgam; however, the corresponding evidence on clinically-manifested adverse outcomes is less consistent. The available reports on mercury-attributed manifestations such as tremor or other neurological conditions did not demonstrate convincingly that the outcomes under question have been caused by the mercury from dental amalgam. As a result, no increased risks of adverse systemic effects (e.g. neurologic, renal) have been clearly established in the general population or among dental professionals. The evidence linking dental amalgam exposure to local adverse outcomes (*e.g.*, lichenoid and allergic lesions of oral mucosa) is stronger, and removal of amalgam fillings does not always result in complete healing. There were also rare reports indicating possible enhanced susceptibility to mercury (and/or other dental amalgam metallic constituents) with subsequent exaggerated immune and inflammatory responses, which may bear resemblance to similar responses to other implantable/insertable devices with metallic components, and the underlying reasons of which are similarly poorly understood. Despite the reasonable assumption that genetic factors such as gene polymorphisms affecting mercury kinetics and excretion may modify individual responses to mercury exposure, the existing evidence on candidate biomarkers is not sufficient to support their use in clinical practices or regulatory considerations.

Overall, although exposure to elemental mercury at sufficiently high levels, e.g., chlor-alkali workers, is associated with adverse human health effects, the current evidence is insufficient to support a causal association between mercury from dental amalgam and reported adverse health effects. This is consistent with the assessments of other scientific organizations such as the recent SCENIHR report (2015, European Union) which concluded that dental amalgam does not pose a health risk for the general population, and the currently available evidence neither precludes the use of amalgam in dental restorations nor suggests the need for preventive removal of pre-existing amalgam restorations. Instead, the SCENIHR report (2015) recognized the need for further research particularly evaluating potential neurotoxicity of mercury from dental amalgam and the possible effect of individual genetic variability on mercury toxicity. Nevertheless, a gap analysis of the existing clinical and biomedical evidence that underlies the currently implemented recommendations regarding dental amalgam suggests the need for continuing assessment of its safety. Most importantly, the emerging evidence on possible *in vivo* transformation of mercury from dental amalgam into methyl mercury and the

subsequent limitations pertaining to mercury speciation analysis (inorganic versus organic mercury) challenge conventional thinking on the origin of mercury found in body tissues. Possible methodological limitations and subsequent inaccuracies in urine and hair mercury measurements (which are currently postulated as the indicators of inorganic mercury and organic methyl mercury, respectively) likely affected the causality analyses aimed to determine the two main sources of exposure, i.e., dental amalgam vs. diet. Specifically, urinary mercury (the biomarker most frequently used to assess dental amalgam exposure in most studies included in the current review) may not be a reliable indicator of mercury released from dental amalgam, especially at a low-level exposure associated with dental amalgam. However, no currently available alternatives have been identified as non-invasive and reliable biomarkers of exposure. A more accurate evaluation of mercury exposure sources (e.g., amalgam vs. diet) is important for addressing the existing knowledge gaps regarding inorganic mercury/methyl mercury toxicity and drawing more definitive conclusions on the causality between dental amalgam and adverse health effects.

In summary, considering the totality of the evidence, including the most recent comprehensive review of clinical studies published since 2010, there is not sufficient evidence of a relationship between clinically detectable adverse health outcomes and dental amalgam mercury exposure, which is consistent with previous analyses conducted by the Department of Health and Human Services (DHHS) and FDA. Notably, there are uncertainties regarding the currently available evidence due to the lack of information on the origin of the various species of mercury. This review identified a scientific need for methodological approaches that would differentiate between inorganic and organic mercury species and thus allow an accurate identification of their initial sources (dental amalgam *vs.* diet). An updated causality analysis using refined mercury exposure indicators and novel risk predictors is needed for further examination of whether documented mercury increases in body fluids would correlate with detectable (clinical or subclinical) manifestations of adverse health effects because of dental amalgam mercury exposure.

Background

Dental amalgam is a dental restorative material that has been used for more than 150 years in the United States for direct filling of carious lesions or structural defects in teeth. Dental amalgam is an intermetallic compound consisting of liquid elemental mercury (Hg) and a powdered alloy composed of silver, tin, copper, and other metals, that are mixed at the point of care to result in a durable restorative material. Approximately 50% of dental amalgam is elemental mercury by weight. Dental amalgam releases low levels of mercury vapor, particularly under stress and abrasion. [1] The diffusion of elemental mercury proceeds through an amalgam oxide layer and saliva into air flowing through the mouth, which is absorbed by the lungs. [2] Other forms or routes of exposure to mercury from dental amalgam include ingestion of saliva containing dissolved elemental mercury and inorganic mercury corrosion products, ingestion of abraded amalgam particles, and embedding of amalgam particles in adjacent soft tissue (amalgam tattoo).

Although millions of amalgam restorations[a] are placed annually [3], there have been concerns, particularly in the last few decades, that exposure to mercury from dental amalgam poses a risk to public health. Beginning in the early 1990s and continuing to the present, the U.S. Department of Health and Human Services (DHHS) and its operating divisions have conducted periodic scientific assessments on the effects of mercury exposure from dental amalgam. Below is a summary of the efforts undertaken and the findings obtained.

Previous Evidence Assessments

1993 Public Health Service (PHS) Report

A major multi-agency review of the available literature, by DHHS, Subcommittee on Risk Management/ Committee to Coordinate Environmental Health and Related Programs (CCEHRP), concluded that mercury released from amalgam does not pose a serious health risk to the general public. [1] The scientific findings of the report can be summarized as follows. Most data suggested that the daily mercury dose was 1 to 5 µg higher for subjects with 7 to 10 amalgams than for persons with no amalgams. Available data were not sufficient to indicate that health hazards can be identified in non-occupationally exposed persons. At mercury doses produced by amalgam fillings, the evidence was not

[a] It should be noted that alternatives to dental amalgam, including dental composite resins, are readily available and widely used. See https://www.fda.gov/medical-devices/dental-amalgam/alternatives-dental-amalgam

persuasive that the wide variety of non-specific symptoms attributed to the fillings and "improvement" after their removal were attributable to mercury from dental amalgam. Conversely, the evidence was not persuasive that the potential for toxicity at the levels attributable to dental amalgams should be totally disregarded. The potential for effects at levels of exposure produced by dental amalgam restorations had not been adequately studied. After review of the literature, the committee recommended that the following research be undertaken to clarify the effects of long-term, low-level mercury exposed from amalgam dental restorations:

- In all studies investigators should analyze and report the species of mercury (i.e., organic, inorganic). This is especially important for measurements in blood. In some cases, analyzing the erythrocytes and serum separately will yield very useful information for interpreting the data when total blood mercury results yield no intelligible relationship.
- Research should be conducted to more precisely define the potential effects from the low levels of mercury exposure due to amalgam dental restoration.

The report also recommended a strategic plan for future research, education, and regulation of dental amalgam including:

- To develop a research agenda for further studies of dental amalgam after consideration of existing studies and knowledge gaps;
- To educate dental personnel and consumers what is and is not known about the safety of dental amalgam;
- To reclassify the components of dental amalgam (mercury and amalgam alloy) into a single classification regulation.

1997 Update to PHS Report

A multi-agency update report, by DHHS, provided a progress update on the strategic plan for future research, education, and regulation for dental amalgam; and included a review of over 150 studies submitted in citizen petitions.{, 1997 #508;, 1997 #508} Consistent with the earlier assessment (1993), this review group found that the cited studies supported that mercury is a well-known toxicant, that its toxicity is dependent on dose, and that mercury from amalgam fillings can accumulate in tissues. However, the data at the time was insufficient to support the petitioners claims that individuals with dental amalgam restorations will experience adverse health effects, including neurologic, renal, or developmental effects.

2004 Life Sciences Research Office (LSRO) Report

A National Institutes of Health (NIH) funded review (LSRO report) of 300 high quality, peer-reviewed studies, published from 1996 through 2003, concluded that there is insufficient evidence to support a

correlation or causal relationship between exposure to dental amalgam and kidney or cognitive dysfunction, neurodegenerative disease, autoimmune disease, or adverse pregnancy outcomes. {, 2004 #509;, 2004 #509} The data at the time did not support a causal association between mercury release from dental amalgam and the various complaints that have been attributed to this restoration material. These data indicate that many individuals presenting with dental amalgam-attributed complaints may suffer from affective symptoms independent of mercury exposure.

2009 FDA Final Rule on Dental Amalgam

Consistent with the objectives of the 1993 PHS report to reclassify the components of dental amalgam (mercury and amalgam alloy) into a single classification regulation, FDA issued a proposed rule in 2002 (67 FR 7620). Following consideration of the comments submitted to the docket (FDA–2008–N–0163) on the proposed rule, FDA issued a final rule for dental amalgam in July 2009, (74 FR 38686). The final rule combined amalgam alloy and mercury components of dental amalgam into a single classification regulation, resulting in a classification of dental amalgam into class II and reclassification of dental mercury from class I to class II, and established special controls (performance data and labeling).{, 2009 #510;, 2009 #510;, 2009 #510;, 2009 #510} In the final rule, FDA relied on valid scientific evidence, including several comprehensive reviews of the scientific literature and safety assessments, air monitoring standards for mercury vapor, biological monitoring standards for urine mercury, and clinical studies. Based on its review of this information, FDA concluded that exposures to mercury vapor from dental amalgam are not associated with adverse health effects in the population age six and older. With respect to potentially sensitive populations, i.e., fetuses, breastfed infants, and children under six years of age, FDA would not expect to see any adverse health effects in these subpopulations from mercury vapors released from dental amalgam, although clinical data are limited. In preparing the final rule, FDA evaluated over 180 peer-reviewed publications and presented its conclusions in a White Paper (see below).

2006/2009 FDA White Paper

In 2006 FDA presented a draft form of its White Paper, which presented FDA's findings regarding the potential adverse health risks associated with exposure to mercury in dental amalgam before the Dental Products Panel and the Peripheral and Central Nervous System Drugs Advisory Committee (the Panel). In 2009 FDA prepared a separate addendum that addressed the Panel's comments. The 2006 draft White Paper and 2009 Addendum constituted FDA's final White Paper, which contained an FDA review

of peer-reviewed amalgam literature published since 1997, and found no new information that would change conclusions of earlier assessments. There was an absence of evidence suggesting that exposure to mercury vapor from dental amalgam is associated with adverse health effects in the population ages six and older. {, 2009 #511;, 2009 #511} FDA also found that the clinical data are limited regarding certain sensitive subpopulations (pregnant women and their developing fetuses, and children under six, including breast fed infants). This report is provided for reference in its entirety on FDA's public webpage for Dental Amalgam.

2010 FDA Review of Mercury Allergies

An FDA review of the peer-reviewed literature was conducted to ascertain the definition, diagnosis, and genetic predisposition to mercury allergy.{, 2010 #512;, 2010 #512;, 2010 #512} The findings of the review were that mercury allergy typically takes the form of localized, delayed-type, cell-mediated cutaneous or mucosal reactions and that other reactions may reflect the irritant nature of mercury in a small number of individuals who are mercury sensitive, although the precise pathologic mechanism of such reactions is unknown.

2010 FDA Systematic Assessment of Peer Reviewed Epidemiologic Literature

FDA conducted a systematic assessment of peer reviewed epidemiologic literature published from 2008 through 2010, to determine whether there was any new information concerning associations between mercury vapor exposure and adverse health outcomes. This report is provided for reference in its entirety in Appendix 1. A summary is provided below.

Thirty-five (35) articles that met the inclusion criteria were categorized per the following focus areas: pregnancy, children, number of amalgams/removal of amalgams, occupational exposure, genetics, hypersensitivity/immunology/autoimmunity, and other. Some studies suggested possible associations between exposure to dental amalgam and adverse health outcomes, as shown by the following findings of interest:

- The number of dental amalgam fillings and number of amalgam surfaces appear to correlate with mercury content in kidney, urine, saliva, and hair. There was also a correlation between the number of maternal amalgam fillings and increased mercury levels in maternal blood, follicular fluid, and cord blood.

- Occupational exposure to mercury among dental professionals was associated with the increases in urinary/blood mercury levels and self-reported prevalence of neurological and psychosomatic symptoms, memory loss, concentration difficulties, fatigue, and sleep disturbance.
- Some patients with symptoms possibly related to mercury from amalgam fillings (e.g., oral lichenoid reactions - OLR) had allergic responses to mercury; many of these symptoms resolved after removal of amalgam fillings.
- Children exposed to dental amalgams had microalbuminuria and incipient increases in the urine concentrations of porphyrins as potential indicators and modifiers of mercury body burden.

However, none of the reviewed studies provided conclusive evidence on the causal associations with dental amalgam. Very little evidence was found regarding thresholds for concern and potential adverse outcomes in pregnant women and children under age six. Overall, the available findings were limited by several concerns such as the lack of proper controls, or small sample sizes. Additionally, most studies were neither sufficiently powered to evaluate rare findings nor had a rationale for the length of follow-up. Most importantly, mercury speciation analysis was not performed in any of the reviewed studies which mostly captured total mercury from all possible sources. The review identified the need for well-designed studies aimed to assess possible effects of mercury from maternal amalgams on health outcomes in children (including developing fetuses and breastfed infants) as well as elucidate immunologic and genetic mechanisms of individual sensitivity to mercury.

Review of Literature Provided in Citizen Petitions Received in 2009-2010

Shortly before and following issuance of the 2009 final rule, FDA received several citizen petitions (dockets FDA-2009-P-0610, FDA-2009-P-0357, and FDA-2014-P-0907) requesting that the agency take several additional actions on dental amalgam, including a ban on the use of dental amalgam as a dental restorative material, restrictions on use in young children, women and particularly women of childbearing age, males, those with compromised kidney, immune, and neurological function, those hypersensitive to mercury, those who test positive for certain candidate biomarkers (e.g., genetic polymorphisms in apolipoprotein E4 or coproporphyrinogen oxidase CPOX4 genes), and other persons within susceptible populations. The citizen petitions also questioned the adequacy of the safety assessment for dental amalgam included in the final rule of 2009. After receiving the citizen petitions, FDA began evaluating the concerns raised, which included review of these petitions and the information

they provided the agency in the form of exhibits (journal articles), directed agency assignments with experts in toxicology and risk assessment, review of the mercury allergy literature, systematic reviews of the amalgam literature (see both above in 2010), and an advisory committee meeting. In December 2010, FDA convened an advisory committee meeting of the Dental Products Panel[b] to gather input from the panel on exposure assessments for mercury vapor from dental amalgam, reference exposure levels (RELs) for mercury vapor, and the adequacy of the clinical studies on dental amalgam. The panel discussed uncertainties with current risk assessments for dental amalgam and believed it would be helpful to have RELs that included data from the most recent studies. The panel also discussed that there may be certain populations that are more sensitive to mercury exposure than the general population. In addition, the panel found that a review of the available literature showed there is no causal link between the use of dental amalgam and various clinically-manifested conditions in the general population. Based on these activities, FDA responded to the citizen petitions filed on dental amalgam in 2015 [c,d,e]. In its response, FDA concluded that the available information does not support the claim that mercury vapor released from dental amalgam is unsafe and results in adverse health effects or the conclusion that dental amalgam presents a substantial and unreasonable risk of illness or injury that would justify a ban[f]. Since September 2015, FDA has received four additional citizen petitions related to dental amalgam. These citizen petitions request restrictions in use, patient labeling, and compliance with international treaties with respect to dental amalgam. No new scientific information is presented in these petitions which was not already addressed in the 2015 response or this assessment. Nevertheless, the Agency is currently preparing a response to the regulatory concerns raised in these citizen petitions.

2012 and 2014 FDA Systematic Assessment of Amalgam Risks in Sensitive Subpopulations

FDA conducted systematic assessments (in 2012 and updated in 2014) of amalgam peer reviewed literature as it relates to health outcomes on sensitive subpopulations. The full reports are provided for reference in Appendix 2. A summary of both systematic reviews is provided below.

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[b] https://wayback.archive-it.org/7993/20170403223455/https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/DentalProductsPanel/ucm235085.htm

[c] https://www.regulations.gov/document?D=FDA-2009-P-0610-0017

[d] https://www.regulations.gov/document?D=FDA-2009-P-0357-0008

[e] https://www.regulations.gov/document?D=FDA-2014-P-0907-0005

[f] Section 516(a) of the Federal Food, Drug and Cosmetic Act and 21 CFR 895.20

For the 2012 systematic literature review, thirty (n=30) articles met the inclusion criteria for assessment. The assessment was focused on articles that evaluated possible risks from exposure to mercury from dental amalgams among three sensitive groups: pregnant women and their developing fetuses; children under six years of age; nursing women and breastfed infants. Available studies (n=11) on pregnant women and their developing fetuses or newborns reported inconsistent correlations between maternal dental amalgams and mercury levels in breast milk or biofluids from breastfed infants and young children. No associations, however, were reported in all three studies that examined adverse health outcomes (other than mercury increases) for these subpopulations. Overall, the review did not reveal consistent evidence suggesting that maternal dental amalgams may increase the risks of health outcomes in pregnant and nursing women, their developing fetuses or breastfed newborns, and children under six years of age. The review, however, suggested that more studies with good data quality, clear definition of health outcomes, and appropriate study designs are warranted for a conclusive evaluation of possible relationships between dental amalgam exposure and adverse health outcomes in the subpopulations under review.

The 2014 literature review update was similarly focused on possible risks from exposure to mercury from dental amalgams among three sensitive groups: pregnant women and their developing fetuses; children under six years of age; nursing women and breastfed infants. Per the update's focus, only one article met the inclusion criteria for assessment. According to the study findings, the child's mental and psychomotor developmental indices showed no clinically meaningful changes among children gestationally exposed to mercury from maternal dental amalgams.

Recent Initiatives

Recently, FDA began a broad initiative to evaluate materials in implanted medical devices to address potential safety questions.{, 2019 #513;, 2019 #513;, 2019 #513;, 2019 #513;, 2019 #513;, 2019 #513;, 2019 #513} Of concern is the issue of the body's response to metal implants; specifically, how to address exaggerated immune and inflammatory reactions to these metals that may occur in certain patients. Dental amalgam, although not an implant[g], is included in this initiative due to possible common features

[g] Dental amalgam is not considered an implant because it is contained within the tooth. The FDA classification panel identified a dental implant as "a device that is surgically placed into, or in opposition to, the maxilla or mandible and which protrudes through the mucosa of the oral cavity" (45 FR 85964). Dental restorative materials such as amalgam do not protrude through the mucosa of the oral cavity and, therefore, are not considered implants. It is considered an external communicating device per ISO 10993/7405.

observed in patients with metal implants and to determine if there is any new evidence that would change the previous conclusions DHHS and FDA have made concerning the risks to health from the use of dental amalgam.

In this report, we present the most recent systematic review of the peer-reviewed literature for studies on dental amalgam involving human subjects.

Evidence Assessment

Purpose

This updated systematic literature review is aimed to assess the recent epidemiologic and clinical evidence on any adverse health effects that were reported in relation to occupational or non-occupational exposure to dental amalgam. Unlike the previous literature reviews (2010, 2012, 2014) which were mostly focused on the amalgam-attributed health outcomes in pregnant women, and their developing fetuses, breastfed infants, and children under six, the current systematic assessment of published literature was aimed to provide a wider evaluation not restricted to certain health outcomes or vulnerable populations. Considering that the FDA's previous systematic review of the published literature was conducted for the 2009 final rule (74 FR 38686) and the corresponding advisory committee meeting[h] took place in 2010, the current assessment was focused on clinical/epidemiological studies published within the time period of 2010- present. The scope of this report is to provide an updated assessment of the most recent epidemiological evidence to determine how it contributes to our understanding of the potential adverse health effects associated with mercury from dental amalgam. This report was not intended to include a quantitative risk assessment, the limitations of which were discussed at the 2010 advisory committee meeting. The current assessment will be used by the Agency to determine if new credible and actionable evidence is available that would impact previous conclusions regarding dental amalgam and to identify any knowledge gaps in need of further study.

Methodology

The search criteria and the entire process of article retrieval and selection are presented in Figure 1.

[h] https://wayback.archive-it.org/7993/20170403223455/https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/DentalProductsPanel/ucm235085.htm

The initial PubMed (Sep 24, 2018) and EMBASE (Oct 5, 2018) queries, with no limits, resulted in approximately 57,000 records. After applying conventional filters for Full Text, English, Humans, and Publication Date (January 1, 2010 through December 31, 2018), the EMBASE/PubMed records were reduced to 1,360 publications, which constituted the pool for 1st pass (*i.e.,* abstract-based) review. The 1st pass review was aimed to include original clinical / epidemiologic studies assessing mercury levels and other outcomes from dental amalgam exposure, while excluding replicate findings and records representing non-original research (*e.g.,* meta-analyses, expert opinions, *etc.*), or research not related to the review's subject (*e.g.,* outcomes evaluating effectiveness and not safety). After the 1st pass review, 200 publications were selected for the 2nd pass (full-text based) review. A total of 185 records (including 3 cross-references from the previous FDA 2010 review and 3 cross-references from the SCENIHR 2015 Report [i]) were selected for the final qualitative evidence synthesis. Note: this review does not include evaluation of amalgam components other than mercury, or perceived amalgam/mercury toxicity outcomes (other than self-reported complaints).

TOXNET databases, including TOXLINE, were queried using similar search strategies; the search results suggested that potential TOXLINE-based publications are retrievable via PubMed and therefore are assumed to be included into the initial PubMed search results. This memo also includes other records (*e.g.,* WHO / SCENIHR reports on dental amalgam, or original non-clinical research, *etc.*) that did not meet the search criteria but were added to support the overall data analysis and interpretation. To distinguish between different types of records, the clinical / epidemiologic publications from initial PubMed/EMBASE searches as well as the cross-references are listed in the References section, while any additional references are presented in the footnotes.

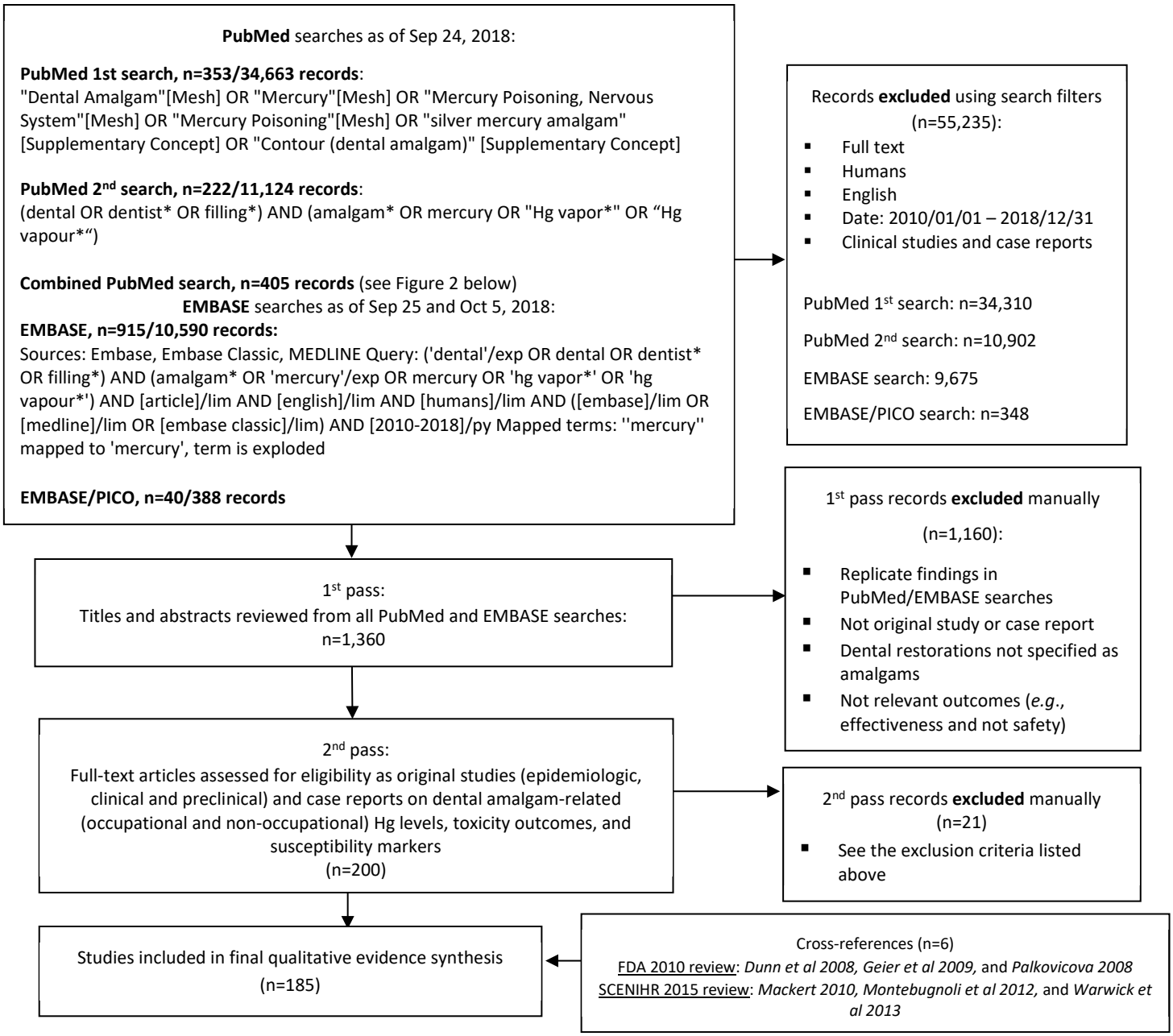
Overview of Studies

Unlike the previous FDA literature reviews (2010, 2014), the current update is not limited to certain adverse outcomes or subpopulations. To cast a wider net that would not be limited to pre-determined adverse outcomes and would incorporate the entire scope of possible (including unknown) adverse outcomes, no outcome-related definitions were included into the search terms. To further ensure comprehensive assessment of possible toxicity outcomes including rare events, the search results encompassed 31 case reports and case series in addition to the main clinical (*i.e.,* case-control, case-

[i] Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR), Scientific opinion on the Safety of Dental Amalgam and Alternative Dental Restoration Materials for Patients and Users (update), 29 April 2015.

case, and cohort) studies. As detailed in the Methodology section, a gradual review using PubMed/EMBASE search filters and manual extraction reduced the initial search results (about 57,000 records) to 179 publications. Three cross-references, which were published after January 2010 (as the cut-off for the current review) and represented clinical evidence on dental amalgam safety, were found in the SCENIHR 2015 Report [i]. Despite being published before 2010, three cross-references from the previous FDA review (2010) were included as positive evidence that counterbalanced some inconsistent findings from the current review, e.g., mercury increases in cord blood [2] and associations with autism [3] as well as possible modifying effects of ethnicity/geographic region [4]. As a result, the final review incorporated clinical and epidemiologic evidence on dental amalgam/ mercury-related toxicity from a total of 185 publications.

Figure 1 Flow diagram of article retrieval and selection



Summary of Evidence

Increased Mercury Levels as a Single or Combined Outcome of Interest

Only a few of the reviewed studies reported no association between dental amalgam exposure and mercury levels in body tissues or biofluids. Negative evidence was mostly limited to relatively small studies measuring the hair mercury levels, which were expected to reflect exposure to methylmercury [5, 6] as well as to studies using unconventional biospecimens such as placenta [7], cord blood [8], or cadaveric brain tissues [9]. In addition, some studies reported inconclusive evidence with no correlation or a relatively weak correlation between the number of amalgam fillings and mercury levels [10, 11]. In some studies, an overall decrease of mercury levels was attributed to reduced use of dental amalgams over the last decades, without providing the actual data on individual exposure to amalgam fillings [12].

Most of the reviewed studies reported elevated mercury levels, when assessing urine samples from dental professionals, or adult and pediatric bearers of dental amalgams. Most studies on *adult populations with non-occupational exposure* reported positive correlation between mercury levels in biospecimens and the number of dental amalgam fillings or surfaces [1, 13-25].

In addition to mercury increases in biospecimens as a single outcome, the increased mercury levels ascribed to dental amalgams were reported in patients with self-assessed complaints [26-28], autoimmune disease [29], multiple chemical sensitivity – MCS [30], and Alzheimer's disease [31].

Similarly, mercury increases in biospecimens positively correlating with the number of amalgam fillings/surfaces were reported in many studies on *pediatric population* [32-39]. Most notably, the two available German studies [40, 41] consistently reported a significant decrease of urine mercury concentrations coinciding with the declined use of amalgam since 1992, after it was no longer recommended for children and women of childbearing age in Germany.

Many *perinatal studies* associated maternal dental amalgam exposure with mercury increases in different biospecimens from both mother and child. In a large study on mothers and their infants [42], the number of mothers' amalgam fillings positively correlated with urinary, blood, and breast milk mercury levels, thereby identifying dental amalgam as one of the main predictors of maternal mercury exposure (along with fish consumption) and supporting the previously derived inference that mercury in

breast milk is predominately inorganic and originates mainly from maternal amalgam fillings[j]. The lack of associations between mercury levels in the breast milk and the infant urine and hair was interpreted as a suggestion that mercury exposure is more likely to occur during pregnancy rather than breastfeeding.

Positive associations between dental amalgams and blood mercury levels in pregnant women were also found by several other studies [37, 43, 44]. Positive correlations between *cord* blood mercury levels and the numbers of maternal amalgam fillings (as well as the years since last filling) were reported [2, 45]. However, some studies found no relationship between dental amalgam treatment (within 6 months) among pregnant women and the cord blood or venous blood mercury levels which were predominantly attributed to methylmercury exposure. [8]

In the study [46] examining possible fetotoxic effects due to unconventional exposure to mercury (*e.g.,* ritualistic practices and folk medicines) in a predominantly Caribbean immigrant population in Brooklyn, NY, about 16% of cord blood mercury levels exceeded the estimated equivalent of US Environmental Protection Agency's (EPA) reference dose (5.8 µg/L); predictors of cord blood mercury included fish consumption and mother's foreign birth, whereas predictors of urine mercury included the number of dental amalgams, mother's foreign birth, and use of special products or remedies that contain mercury.

A correlation between maternal amalgam fillings and mercury levels in breast milk (including colostrum and transitional milk) was shown in two studies [47, 48]. In a study on lactating mothers from the Western Amazonia region [49], an area characterized by high fish consumption and prolonged breastfeeding, the proportion of inorganic mercury in milk was higher among urban mothers with higher numbers of amalgam fillings than in women who did not have many amalgam fillings; however, no significant correlations between mercury levels and either amalgam fillings or daily fish consumption were found. No mercury increase in breast milk was reported in a study where most women (64%) did not have amalgam fillings. [50]

Despite being postulated as an indicator for methylmercury, the concentration of mercury in a woman's hair correlated with the placement time and number of amalgam fillings as well as with pregnancy interval and lactating period [51, 52]. No significant association between maternal hair mercury levels

[j] Oskarsson, A., Schultz, A., Skerfving, S., Hallen, I. P., Ohlin, B., & Lagerkvist, B. J. (1996). Total and inorganic mercury in breast milk in relation to fish consumption and amalgam in lactating women. Archives of Environmental Health, 51, 234–41.

and the presence of amalgam fillings was found in a study where only 13.4% of mothers had exposure to dental amalgam. [5]

Consistent with the aforementioned WHO 2010 report [i] on dental materials {Petersenm, 2010 #515} , which stated that the presence of methylmercury in breast milk is not sufficient to outweigh the benefits of breastfeeding, the mercury concentrations attributed to dental amalgam in most of the reviewed studies were not sufficient for challenging overall safety of breastfeeding in the general population (if devoid of excessive fish/seafood consumption, or unconventional sources of mercury exposure such as some folk medicines or ritualistic remedies).

Among the studies investigating *occupational exposure* to elemental mercury vapor from amalgams, higher mercury levels (as a single outcome) in dental professionals compared to non-exposed control subjects were reported in several studies [53-57]. In addition, the elevated mercury levels due to occupational exposure were reported in studies assessing other outcomes, including self-assessed health complaints [58], multiple sclerosis and/or tremor [59, 60], neurocognitive symptoms [61], peripheral nerve function [62], pregnancy-related outcomes [63], and subclinical markers [64-67].

A dose-response relationship reflecting occupational exposure in dental professionals was suggested by positive associations between mercury concentrations and factors such as duration of working in dental practice, number of placed/removed amalgams, and use of heated copper amalgam or reusable capsules *vs.* encapsulated amalgam [55, 68-70]. Elevated mercury levels were associated with occupational hygiene behavior and certain non-standard practices, *e.g.,* use of squeeze cloths [71], or open-toed footwear [68]. In the bench study examining mercury vapor levels in ambient air during amalgam removal, as typically performed in dental training [72], 36% of the mercury vapor readings exceeded the absolute ceiling value when neither water spray nor suction was used. As a result, amalgam removal during training was suggested to be performed only while using water spray and high-volume suction; alternatively, dental students were suggested to use appropriate personal protective equipment.

Levels of mercury reported for dental professionals vary globally. While the increased mercury levels among dental professionals compared to non-exposed controls (about 23-30 and 3 µg/L in blood, respectively) were limited to the relatively small cohorts from certain locations (*e.g.,* Lahore, Pakistan [73]), a large Norwegian study on the long-term trends in occupational mercury exposure reported that

mercury levels were higher in the 1960s-1970s and decreased gradually thereafter [70]. In most of the reviewed studies conducted outside the US, the reported mercury levels cannot be expected to be fully representative of occupational exposure to dental amalgams in the US. Studies conducted among US dental professionals [62, 69, 74-76] reported moderately elevated mercury levels, overlapping with levels found in the general population. In the large study on dentists (n=13,906) recruited via the American Dental Association [59], urinary mercury concentrations decreased by 90% during the screening program spanning from 1976 to 2012: 20.1 µg/L (95% CI: 14.0; 26.2) and 2.04 µg/L (95% CI: 1.87; 2.22), respectively. Despite the marked reduction, urinary mercury levels among dentists in 2011-2012 were still higher compared with the National Health and Nutrition Health Examination Survey (NHANES) population: 1.69 µg/L (95% CI: 1.58; 1.81) and 0.66 µg/L (95% CI: 0.54; 0.78), respectively. The elevated mercury levels among dental professionals were shown to reflect exposure not only from dental amalgams handled in the occupational setting, but also from personal amalgam fillings in dentist's mouth [58, 69, 73], with the latter explaining a large portion of interindividual variance and being a better predictor of urine mercury increase [69].

Thus, based on overall evidence on mercury measurements in relation to both occupational or non-occupational exposure, increased mercury levels can be identified as the most plausible *subclinical* outcome associated with dental amalgam. However, evidence on the associations between dental amalgam and increased mercury levels in certain biofluids such as cord blood or breast milk is less consistent. Possible associations between increased mercury levels and *clinically-manifested* health outcomes in relation to dental amalgam remain to be elucidated.

Consistent with the current FDA 2018-2019 systematic literature review, the FDA 2010 review concluded that "the number of dental amalgam fillings and number of amalgam surfaces appear to correlate with mercury content in kidney, urine, saliva, and hair (see Appendix 1 (page 73)). There was also a correlation between the number of maternal amalgam fillings and increased mercury levels in maternal blood, follicular fluid, and cord blood". The FDA 2012 review update provided further "evidence in support of an association between the number of dental amalgams/surfaces in pregnant women and the Hg levels in the women and their developing fetuses or newborns" (see Appendix 2 References no.11,13,14,16-23). The FDA 2006/2009 White Paper and Addendum **[**7], based on a review of over 200 published studies, concluded that (i) individuals with amalgam restorations generally have urinary mercury concentrations that are higher than individuals with no amalgam; however, these

concentrations are lower than those concentrations associated with adverse outcomes resulting from high occupational exposures to mercury vapor", and (ii) "dental professionals … generally have higher urine mercury levels than patients; however, the weight of evidence …does not suggest adverse effects resulting from [dental amalgam-related] exposures".

Similarly, external reviews such the LSRO 2004 report [5], a scientific review developed under contract for the Trans-agency Working Group on the Health Effects of Dental Amalgam and based on a review of 300 published studies, stated that "based on most surveys published since the beginning of 1996, mean HgU [urine mercury] values for the general population are <2 µg Hg/L. In addition, 95% of individuals in the general population have HgU values at or below the WHO estimate of approximately 4-5 µg Hg/L". Despite the demonstrated "positive correlation between the number of dental amalgam restorations or surfaces and urine mercury concentrations in non-occupationally exposed individuals," the available data were found to be "insufficient to support an association between mercury release from dental amalgam and the various complaints that have been attributed to this restoration material."

Thus, slightly increased mercury levels (at or below the WHO reference level) constituted one of the outcomes most frequently reported in relation to dental amalgam; however, despite the consistency of this subclinical outcome, its translation into clinically manifested adverse outcomes remained unclear throughout the reviews, as discussed below.

Self-assessed Health Complaints and Other Health-related Measures

Most of the studies investigating health complaints attributable to mercury toxicity reported some positive evidence in relation to dental amalgam exposure. A study identified musculoskeletal pain, sleep disturbance, and fatigue as the most commonly reported complaints among the Swedish patients with perceived adverse reactions to dental restoration (whose health-related quality of life was assessed as significantly lower compared to the general Swedish population). [77] Although ill health attributed to dental materials was associated with higher sick-leave numbers and dependence on benefits, replacement of dental amalgam fillings with alternative restorations did not seem to alleviate health complaints and improve workforce participation [78]. A study pertaining to occupational exposure [79] examined mortality risk over three decades (1960s-1980s) in the offspring of Swedish female dental professionals. During the 1960s with supposedly the highest mercury exposure, the risk of neonatal

mortality was found to be higher for sons of dental nurses *vs.* sons of assistant nurses: (Hazard Ratio) HR=1.82 (95% Cl: 1.04, 3.22). However, no risk increases were found for the subsequent decades, with a consistent risk decrease over the three decades (HR=0.63, 95% CI: 0.44, 0.90).

Decreased frequency and/or intensity of health complaints (*e.g.*, musculoskeletal pain, gastrointestinal symptoms, fatigue) after removal of amalgam restorations was reported [26, 80]. A relatively small study (total – 40 subjects) identified no stable correlations between the decreases in serum and urine mercury levels and the changes in health complaints after removal of amalgam fillings. [81] However, in a larger study (total – 955 subjects), removal of amalgam fillings was associated with decreased urine mercury levels and improved self-reported symptoms related to memory loss, shakiness in hands, coordination, and stomach problems. [28] Similarly, another study showed post-amalgam filling removal decreases in plasma and urine mercury levels, along with the reduced score of various subjective symptoms in patients with *vs.* without removal of amalgam fillings [27] . The study, however, could not determine if some personality 'abnormalities' have predisposed to amalgam-related complaints, or if they were a consequence of amalgam-related mercury exposure.

Inconsistent results were reported in two studies evaluating health complaints or hospital admissions related to occupational exposure. In a study from Iran, some self-reported symptoms (*e.g.,* respiratory disorders, irregular pulse, hand tremor, spasm of the upper extremities, moodiness, nervousness, anxiety, insomnia, memory deficit, depression and chronic fatigue) were found to be more prevalent among dentists compared to general practitioners, with the daily numbers of handled amalgam fillings positively correlating with muscular and neuropsychological symptoms in particular *[58]*, (Note: occupational exposure in this study might have been affected by a significantly higher number of dentists with their own amalgam restorations *vs*. controls). In a Norwegian study that evaluated hospital admissions, no positive associations were found for the discharge-based risk for neurological diseases among dental professionals. [82] However, while admissions for renal diseases showed an increase during periods with less mercury exposure among dental assistants, an increasing risk trend for renal disease in relation to employment length was found among dentists.

Thus, evidence linking possible mercury toxicity from dental amalgam to self-assessed health complaints and other health-related measures such as hospital discharges remains inconsistent. A relatively higher prevalence of self-reported symptoms in some studies may be affected by modifying factors such as the

study's country of origin or time period that may reflect differences in dental care and amalgam handling practices.

Similar to the current FDA 2018-2019 assessment, the FDA 2010 review (see Appendix 1) found that "occupational exposure to mercury among dental professionals was associated with the increases in urinary/blood mercury levels and self-reported … neurological and psychosomatic symptoms, memory loss, concentration difficulties, fatigue, and sleep disturbance." However, the causality of these symptoms has been consistently characterized as uncertain. The PHS 1993 Report [1] stated that "at the mercury doses produced by amalgam fillings, the evidence is not persuasive that the wide variety of non-specific symptoms attributed to fillings and "improvement" after their removal are attributable to mercury derived from the fillings". Similarly, the LSRO 2004 report [5] cited the World Health Organization & International Programme on Chemical Safety (1991) stating that "exposure to mercury vapor (Hg^0) from dental amalgam causes a constellation of varying and nonspecific complaints…[such as] fatigue; depression; muscle, joint, or tendon pain; weakness and dizziness; metal taste; headache; anxiety; impaired sensory function; loss of mental concentration and forgetfulness; sleep disorders; decreased sexual function; and gastrointestinal distress." However, the LSRO 2004 report [5] characterized these complaints as "quite broad and nonspecific compared to the well-defined set of effects that have been documented for occupational and accidental Hg^0 exposures (*i.e.,* tremor, stomatitis, gingivitis, ataxia, hearing loss, renal impairment, and emotional instability and irritability)", suggesting that "many individuals presenting with dental amalgam-attributed complaints may suffer from affective symptoms independent of mercury exposure".

Thus, the evidence of self-assessed health complaints was consistently assessed as not supportive in terms of their relevance to mercury from dental amalgam.

Oral Mucosa and Cutaneous Outcomes

Oral mucosa lesions were the most frequently reported outcomes pertaining to dental amalgam. Amalgam tattoos were described as the most common lesions among generally uncommon pigmented oral mucosa lesions [83, 84]. In the large study examining oral mucosa lesions among 1,275 patients attending university-related dental clinics over a one-year period [85], pigmentations were identified in 30.2% of all-comers, among which amalgam tattoos accounted for 18.9% and heavy metal deposits – for

0.26%; oral mucosal pigmentation caused by heavy metals (including mercury) was described as a bluish-black line, known as Burton's line, reflecting gingival inflammation. In the longitudinal Brazilian study on 34,127 histopathological specimens logged over a 64-year period, only 1.34% represented pigmented oral mucosa lesions [83], with amalgam tattoo as the most frequent histopathological diagnosis (46.3%); however, the frequency of amalgam tattoos decreased from 11 cases in 1998 to 4 cases in 2016. Overall, amalgam tattoos remained the most common oral lesion reported in the reviewed clinical studies and case reports as well. About two thirds of the reviewed case reports reported amalgam tattoos in women, with some studies confirming the predominance of female (and older) patients. [86]

Amalgam tattoos usually occur when small amalgam particles are inadvertently implanted into oral soft tissues during dental procedures [87]; amalgam tattoos usually appear as asymptomatic black, blue, or gray macules (<1 cm) located on the gingiva, alveolar, buccal mucosa, or the oral cavity floor. Microscopically, two kinds of lesions may frequently co-exist in the same amalgam tattoos: the irregular, dark solid fragments of metals, or the fine, brown or black, granules dispersed between collagen bundles and around small blood vessels and nerves [87]. Histological examination may be necessary for differentiating amalgam tattoos from other pigmented mucosal lesions such as malignant melanoma, especially in cases with a personal history of melanoma [88]. The amalgam-related granular material distributed in the interstice and macrophages is not expected to stain with iron or melanin stains [89]. Amalgam tattoos can be accompanied by macrophage-mediated and other chronic inflammatory reactions indicating the amalgam-induced tissue responses such as foreign body granuloma with multinucleated giant cells and thus demonstrating similarity to histopathological manifestations associated with other, especially metal, biomaterials[k]. [87] As a further similarity, the amalgam-related metal release is currently attributed to amalgam corrosion rather than the old concept of electrochemical reactions between metals with different electric potentials.[90]

Some amalgam tattoos were reported to develop as soon as within 3 months after placement of amalgam restorations [91]. In most cases, amalgam tattoos remain asymptomatic, with their removal mostly prompted by esthetic and not medical reasons, except the cases complicated by lichenoid reactions [92]. There is a reported case of an amalgam tattoo, which remained asymptomatic for

[k] Anderson JM, Rodriguez A, Chang DT. Foreign body reaction to biomaterials. Semin Immunol. 2008 Apr;20(2):86-100. Epub 2007 Dec 26. Review.

decades but was eventually removed due to concerns for the increasing halo. [93] Additionally, a rare case was reported for which the amalgam tattoo removal resulted in improvement of the recurrent sinusitis, which was speculatively associated with the immune sensitization by amalgam tattoo particles.[94]

The next group of oral mucosa lesions frequently described in relation to dental amalgam were oral lichenoid lesions (OLL), including oral lichenoid planus (OLP) and oral lichenoid (contact) reaction (OLCR). Although the amalgam-related oral mucosa reactions are relatively rare compared to various cutaneous allergic reactions [95], they are suggested to share the same contact allergy-related immunological basis, *i.e.,* an excessive antigen-mediated response, which may lead to tissue damage. Hypersensitivity reactions may be accompanied by histopathological features of lichenoid mucositis and contact allergy to mercury may correlate with the incidence of OLL in association with symptoms such as burning mouth, xerostomia, and orofacial granulomatosis. With the underlying mechanisms not entirely clear, the amalgam-associated OLLs may represent true delayed (type IV) hypersensitivity with a trans-epithelial route of entrance of the metal haptens released from dental restorative materials. Clinically, OLLs were mostly described as asymmetrical and asymptomatic white papules or macules in the buccal mucosa [95, 96]. While many OLLs were described as having no direct contact with amalgam restorations, some lesions were found near old and corroded amalgam restorations [97].

Since OLLs carry a potential risk of malignant transformation, some authors mentioned that amalgam restorations are frequently removed in cases when patch test results are positive for the amalgam-related allergens; the amalgam-related OLLs are expected to be resolved after removal [95], [98]. Addressing the clinical need for differentiating between idiopathic OLP and amalgam-related lichenoid lesions, some authors [99] suggest the term of OLCR for designating cases that stand to benefit from amalgam replacement, being spared the anxiety of potential malignant transformation risk attached to idiopathic OLP; the clinically-diagnosed OLCR was suggested as a more reliable indicator for considering amalgam replacement, compared to patch testing.

Some studies [100-102] found patch testing more useful for assessing delayed contact hypersensitivity, when considering amalgam removal in patients with OLL of unclear etiology. However, even in the studies that advocated for use of patch testing as a guiding tool when considering the replacement of amalgam restorations, mercury positivity was found in less than a half of tested patients, *e.g.,* 32%

[100]), 39% [103], and 44% [102]. Furthermore, many OLL cases did not benefit from removal of dental restorations, e.g., no improvement was reported in 35% [98].

In the study comparing prognosis and regression of OLCR and OLP after replacement of dental (mostly, amalgam) restorations [103], patch testing with dental screening series revealed positive reactions to mercury in 39% of tested patients. After replacement, regression of the oral lesions was more pronounced among patients with OLCR. As no cases assessed as OLP completely regressed after the replacement, the authors emphasized the importance of a proper diagnosis to avoid unnecessary removals of intact restorations on patients with OLP. To distinguish between the amalgam-related OLCRs, the term OLP was suggested to be reserved for the lesions that exceed the contact zone or completely lack contact with dental restorations. As such, the term OLP was limited to mucosal lichenoid planus as a chronic systemic disease with immunity-related pathogenesis, which rarely undergoes spontaneous remission. Contact with amalgams and positive patch testing were described as good but not absolute indicators of the expected beneficial effect of amalgam replacement, mostly among cases described as OLL, but not OLP [104]; however, clinical healing was not always associated with the corresponding histopathologic healing of OLL/OLP lesions.

In addition to local allergic and inflammatory reactions affecting the oral mucosa, dental amalgam fillings were associated with oral granulomatosis [105, 106], which represents chronic granulomatous inflammatory reaction with lip swelling.

Dental amalgam related cutaneous manifestations may involve generalized atopic or contact dermatitis including eczema and pruritis, with or without oral mucosa reactions [90, 107-110]. A large study [101] evaluated the utility of patch testing for confirming possible association with dental restorations and assessing the benefits of replacement of amalgam restorations; ammoniated mercury and amalgam were identified as some of the most frequent dental series allergens among the entire study population comprised of OLR, treatment-resistant OLP, and atypical lichenoid features. Among the patients with amalgam fillings, 29.6% reacted to ammoniated mercury, 26.5% to amalgam, and 4.1% to amalgam alloying metal. Based on moderate to complete resolution in 81% of the patch test-positive patients who underwent replacement of amalgam fillings, patch testing was rendered as a reliable tool for identifying an OLR caused by contact hypersensitivity.

Some cases of OLL (also described as oral leukoplakia) in patients with amalgam restorations were discussed in the context of potential risk of malignant transformation. [95] In a study that examined intraoral metal contact allergy as a possible risk factor for oral squamous cell carcinoma (SCC) [111], patients with oral SCC tended to have a higher likelihood of metal contact allergy, especially to mercury which was present in dental restorations adjacent to their oral SCC. Although these results might have been affected by a relatively small sample and heterogeneity between the study groups, mercury sensitivity was suggested to contribute to development of oral SCC, along with the known risk factors such as tobacco or alcohol use.

A study reported dental technicians with *vs.* without occupational contact dermatitis were more often diagnosed with allergic dermatitis (37.6% *vs.* 18.5%; P=0.0002). [112] However, patch testing revealed that the most frequent positive reactions were to methacrylates / acrylates, with positivity to the amalgam and ammoniated mercury found only in 4 and 3.7%, respectively. Unlike clinical relevance for patients with OLP lesions at the site of amalgam fillings, the relevance of patch testing was found questionable for identifying amalgam-related allergens among dental workers. The authors raised further doubts about the need for routine patch testing with dental metals series in all cases with occupational contact dermatitis, suggesting that it may be needed only in cases with suspected metal allergy.

Thus, despite their relative rarity, oral mucosa lesions (especially amalgam tattoos) represent local clinical manifestations that are most frequently reported in relation to dental amalgam. Further, some amalgam tattoo related histological features resemble foreign body responses in periprosthetic tissues and thus underscore pathogenetic similarity of possible adverse tissue reactions to dental amalgam and metal implants. As another similarity, both dental amalgam and metal implants may elicit cutaneous allergy which is frequently attributed to *metal allergy, or sensitivity*; however, its true pathogenetic mechanisms as well as its predictability by skin patch testing remain to be elucidated.

Similar to the current FDA 2018-2019 assessment, the FDA 2006/2009 White Paper and Addendum [7] stated that “various types of lesions of the skin, mouth, and tongue might sometimes occur as a result of mercury-containing amalgam. The skin conditions include nummular dermatitis, oral lichenoid planus, gingivostomatitis, ulcers, various mucosal changes, burning mouth syndrome, orofacial granulomatosis, erythema, swelling, itching, and pigmentation”; “hypersensitivity or allergy to mercury, often indicated

by patch-testing" was suggested "as the likely cause of the dermatologic reactions." The review concluded that "when dental amalgams are removed from patients with mercury allergy or other immune-related responses, the conditions often resolve." As stated in the FDA 2010 systematic review (see Appendix 1), "some patients with symptoms possibly related to mercury from amalgam fillings (*e.g.,* oral lichenoid reactions - OLR) had allergic responses to mercury; many of these symptoms resolved after removal of amalgam fillings". As further detailed in the FDA 2010 review, "mercury allergy typically takes the form of localized, delayed-type, cell-mediated cutaneous or mucosal reactions"; in addition, "other reactions may reflect the irritant nature of mercury in a small number of individuals who are mercury sensitive."

The external PHS 1993 report [1] similarly stated that "allergic reactions to amalgam [may] involve skin reactions, such as rashes and eczematous lesions". The LSRO 2004 report [5] also concluded that "dental amalgam is capable of producing delayed hypersensitivity reactions [which] usually present with dermatological or oral symptoms. For individuals exhibiting positive patch tests, the removal of dental amalgam restorations and their replacement with composite materials may promote the resolution of the observed symptoms". As specified by the LSRO 2004 report, only "a small portion of the human population demonstrates this allergic sensitivity".

Although the oral mucosa/cutaneous lesions represented one of the most consistently assessed findings in relation to dental amalgam, many of these lesions (e.g., amalgam tattoo) are less clinically meaningful, compared to more serious complications potentially attributable to mercury (e.g., neurotoxicity). Despite potential relevance of mucosal/cutaneous lesions of allergic nature to overall implant/insert reactivity, their causal relationship to dental amalgam remains questionable in many cases (e.g., when removal of dental amalgam fillings does not result in healing).

Systemic Inflammation and Autoimmunity Related Outcomes

In addition to allergic mechanisms, some of the studies on dental amalgam examined possible relevance to systemic inflammation and autoimmunity. In the study on patients with systemic lupus erythematosus [113], urinary mercury was not associated with disease activity or damage, and hair mercury showed negative correlations with both indices, thereby providing no support for an adverse association between dental amalgam-related mercury exposure and lupus.

In a study examining mercury exposure among patients with symptoms indicative of chronic mercury toxicity [29], blood and urine mercury levels were relatively elevated in subjects with oral lesions, autoimmune disorders, and multiple sclerosis. A statistical difference with regards to the number of amalgam fillings was found in subjects reporting autoimmune diseases (P=0.0317) which were diagnosed more frequently in the group with >10 amalgams, compared with those with 6-10 or 0-5 amalgams (26.3% compared to 5.6% and 0%, respectively). A correlation between the number of amalgam fillings and mercury levels was observed. After adjusting for age and sex, no association was reported between amalgam fillings and multiple sclerosis or other autoimmune diseases. In the study examining possible association between dental amalgam and Hashimoto disease [114], no statistical difference was found between the frequencies of dental amalgam fillings among patients with Hashimoto's thyroiditis and healthy controls.

In the study with a small cohort of patients with Multiple Chemical Sensitivity (MCS; defined as a chronic condition with an exaggerated response to environmental toxicants)[II], which was perceived to be associated with mercury toxicity, patch testing and lymphocyte transformation test (LTT) identified allergy to mercury and other amalgam-related metallic components in 50% and 84.6% subjects, respectively. [30] The presence of dental amalgam fillings among MSC patients was associated with increased prevalence of metal allergy (along with higher mercury levels detected in different biofluids and tissues); chronic fatigue syndrome and fibromyalgia were reported as the most frequent diagnoses (26.8% each).

Among the studies examining autoimmunity-related markers, oral metal exposure (including the presence of amalgam fillings) was not significantly associated with any of serological phenomena.[115] In the study investigating a possible association between mercury exposure and antinuclear antibodies (ANA) [116], ANA positivity was found in 16% of the tested women of reproductive age; 96% of the ANA-positives had a nuclear speckled staining pattern. However, mercury exposure due to dental amalgam fillings was not specified, and ANA positivity (which was associated with the hair and blood, but not urine, mercury levels) was attributed to methylmercury exposure.

[II] MCS is not recognized as an organic, chemical-caused illness by the World Health Organization, American Medical Association, or any of several other professional medical organizations

In addition, some case reports suggested possible links between dental amalgam exposure and systemic autoimmune/inflammatory conditions such as vascular myopathy [117], Autoimmune/inflammatory Syndrome Induced by Adjuvants (ASIA) [118], sarcoidosis [119], chronic fatigue syndrome, fibromyalgia, and various connective tissue diseases [120-122].

Overall, evidence linking mercury toxicity from dental amalgam to possible systemic inflammatory/immune responses was inconsistent and did not originate from robust clinical studies with appropriate control groups and study endpoints.

The FDA 2010 systematic review (Appendix 1) provided a combined assessment of Hypersensitivity/ Immunology/ Autoimmunity related outcomes, most of which were related to allergy; no evidence of immunotoxic effects due to dental amalgam exposure was found per a single cited study which assessed specific serum antibodies to anti-glomerular basement membrane.

Among external reports, the LSRO 2004 report [5] stated that "insufficient research was done to support or refute the hypotheses that dental amalgam causes…any autoimmune disease, including multiple sclerosis". The SCENIHR 2015 Report [i] on the safety of dental amalgam and alternative restorative materials similarly reported "no evidence that autoimmune disease is provoked in humans by mercury exposure from amalgam fillings"; with regard to systemic inflammation, the report stated that "there is some evidence that exposure to mercury influences proinflammatory cytokine levels, but the clinical implications are not clear".

Although possible systemic inflammation/autoimmunity related outcomes have been ascertained in relation to overall implant/insert reactivity, no reliable evidence on the relevance of this category to mercury from dental amalgam was found throughout the reviews.

Neurological and Neuropsychological Outcomes

Many of the reviewed studies assessed neurological (including neuropsychological and neurodevelopmental) outcomes that were assumed to more likely reflect mercury toxicity, as suggested

by Minamata disease[m] , which resulted from environmental pollution by inorganic mercury and its subsequent transformation to methylmercury through the food chain. In addition, poisoning by mercury vapors (which may involve extreme cases of occupational exposure in dentistry) may cause so called erethism syndrome[n] which starts with behavioral and cognitive symptoms such as irritability, anxiety, mood lability, impaired sociability, depression, and memory loss and may result in fine tremor and polyneuropathy with continuing mercury exposure [61].

In the Brazilian study on occupational mercury exposure in dental professionals [61], memory loss, insomnia, tingling, and numbness constituted the most frequent (neuro)cognitive complaints compatible with mercury contamination; some symptoms were reported to correlate with exposure time or number of placed amalgam fillings (with no further details). In the study on occupational mercury exposure among Tunisian dentists [60], the questionnaire-based scores of neurological symptoms, memory disturbances, and anxiety levels were found to be significantly higher compared to non-exposed controls; in the dentists with urinary mercury levels >35 µg/g-creatinine (n=9), neurological examination revealed tremor in upper limbs. However, no substantial changes in relation to the motor and memory-related functions were found in the Norwegian study on possible adverse neuropsychological effects in female dental personnel [123]. In the Swedish study investigating possible adverse effects due to maternal occupational mercury exposure during pregnancy [124], sons of female dental workers had similar or higher cognitive function test results, compared to their matched controls. In another Swedish study on occupational exposure [125], no evidence of elevated risks for neurological diseases or intellectual disability were found among sons of female dental *nurses*; the corresponding results among female *dentists* remained unclear due to a low number of events.

No substantial changes in peripheral nerve function in relation to mercury levels were found among US dentists [62]. In another study on US dentists [59], no clinically meaningful associations were found with the occurrence of multiple sclerosis. However, its prevalence among US dental professionals was estimated to be slightly higher (183 per 100,000), compared to the general US population (130 per

[m] Lessons from Minamata Disease and Mercury Management in Japan (2013). Ministry of the Environment, Japan (https://www.env.go.jp/chemi/tmms/pr-m/mat01/en_full.pdf; accessed Jan 15, 2019).
United Nations Environment Programme. (2013). Minamata convention on mercury. Geneva, CH: Unep.

[n] Carocci, A., Rovito, N., Sinicropi, M. S., & Genchi, G. (2014). Mercury toxicity and neurodegenerative effects. Reviews of Environmental Contamination and Toxicology, 229, 1-18.

100,000 per the National Society for Multiple Sclerosis 2009 Report, as cited by the authors); in addition, urinary mercury and cumulative mercury exposure were linked to a slightly increased tremor risk.

A study on non-occupational mercury exposure in relation to multiple sclerosis [126] derived similarly equivocal results: the presence of amalgam fillings was associated with significant changes in some Expanded Disability Status Scale scores among patients with multiple sclerosis, but further interpretation was complicated by a small sample size (n=33). Among other studies investigating neuropsychological outcomes due to non-occupational exposure in adults with dental amalgams, compared with controls, it was reported that the study subjects with amalgam-related complaints had more self-assessed symptoms, mainly musculoskeletal and neuropsychological; however, no significant difference in cognitive tests was found between the amalgam and control groups. [127]

Further, in one study, individuals with amalgam fillings had a slightly higher likelihood of Alzheimer's disease than subjects without amalgam fillings: OR=1.105 (95% CI: 1.025, 1.190). [31] In another study, individuals with amalgam fillings also had a higher risk of Parkinson's disease (adjusted HR=1.58, 95% CI: 1.12, 2.23; P=0.009). [128] Among subjects with amalgam fillings, diabetes or hyperlipidemia were shown to lower HRs for Parkinson's disease, while hypertension was shown to increase it substantially (HR=1.645; 95% CI: 1.098, 2.464; P=0.016). After adjusting for comorbidities, the patients with dental amalgams were 1.6 times more likely to have Parkinson's disease compared to their non-exposed counterparts. The probability of Kaplan-Meier disease-free survival was higher in the cohort without *vs.* with amalgam fillings. Referring to possible methylation of inorganic mercury by the host's microflora, the authors posited that mercury from dental amalgam may be biomethylated into methylmercury, a potent neurotoxic form of mercury that effectively crosses the blood-brain barrier, which may contribute to neurodegenerative diseases such as Parkinson's disease.

Many of the pediatric studies on dental amalgam exposure focused on autism and autism spectrum disorder (ASD). In the study [3] mentioned in the FDA 2010 review, numbers of maternal amalgam fillings were associated with different severity levels of autistic disorders among their offspring: children born from mothers with ≥6 dental amalgams during pregnancy had 3.2 times greater odds of being diagnosed with autism (as a severe form) *vs*. an ASD (as a mild form), than children with ≤5 maternal amalgams (P=0.0127). In addition, higher plasma mercury levels among children with ASD *vs.* controls were speculatively attributed to possible prenatal amalgam-related exposure, based on a higher

frequency of current amalgam restorations among their mothers [129]. However, an increasing trend for mercury levels in relation to maternal amalgam fillings did not reach significance in a study that showed a significant difference in the hair mercury levels among autistic children *vs.* controls.[130] In a study that investigated possible associations between porphyrins and mercury exposure, autistic children had elevated levels of some urinary porphyrins, in comparison to neurotypical children or children with pervasive developmental disorder.[131] However, no differences between autistic and neurotypical children were found in relation to their current urinary mercury level or past mercury exposure, which included both personal and maternal (during pregnancy) amalgam history. No significant differences in urinary mercury levels among ASD children *vs.* controls were reported, regardless of controlling for number of amalgam fillings.[132] No evidence suggesting adverse effects of prenatal mercury exposure on children with autism was found in a study where an increased maternal exposure to mercury from dental amalgam was associated with *lower* rates of poor sociability, and poor social cognition was found among children whose mothers ate no fish. [133] Similarly, autistic/ASD children were reported to eat less fish, in a study that also did not find any evidence linking autism/ASD in subjects with dental amalgams. [134]

There was a report of no differences pertaining to blood mercury levels or maternal dental fillings among children diagnosed with motor and mental developmental disabilities, epilepsy, attention deficit/hyperactivity disorder and autism, compared to healthy controls.[135]

In two studies that investigated possible neuropsychological and psychosocial effects in children with various dental restorations, no adverse outcomes were observed in subjects bearing amalgams *vs.* composite restorations. [136, 137] Further, some borderline trends indicated slightly poorer test results on intelligence, achievement, or memory among children with composite restorations, whereas subjects with amalgam fillings were associated with some nonsignificant, but slightly improved scores [136]. Similarly, subjects with amalgams showed some improvement in interpersonal relations, self-reliance, anxious/depressed, and delinquent behaviors compared to subjects with composites [137]. As a result, no evidence was found supporting the need for systematic removal and replacement of dental amalgams with resin-based composites, especially considering potential risk from the removal-related transient increases in plasma mercury concentrations.[137]

No consistent evidence linking amalgam-related prenatal mercury exposure to neurobehavioral consequences was found in retrospective analyses based on the Seychelles Child Development Study, which was initially aimed to examine mercury exposure among inhabitants of Seychelles islands with traditionally high fish consumption. [138-140] One study found no significant adverse associations between number of prenatal maternal amalgam surfaces as a primary metric (with or without adjustment for pre/post-natal methylmercury exposure) and any of the tested neurodevelopmental outcomes in children at 66 months of age; analyses using prenatal maternal amalgam occlusal point scores as a secondary metric showed a single adverse association (the letter word recognition subtest of the Woodcock-Johnson tests of achievement) for boys and some seemingly beneficial associations for girls. [139] Another reported no significant associations between number of maternal amalgam surfaces and mental and psychomotor development per the Bayley Scales of Infant Development-II (at 9 and 30 months). [138] One study reported that neither metric (surfaces or occlusal points) used for evaluation of the amalgam status during pregnancy was associated with any outcome per age-appropriate testing of the cognitive, language, and perceptual functions, and scholastic achievement in children at 5 years of age. [140] In a prospective clinical trial with 7-year follow up, no consequential differences except non-significant changes involving tremor and some other neurological signs were found among children treated with dental amalgam *vs.* resin-based composites. [141]

Overall, evidence regarding possible mercury neurotoxicity due to dental amalgam remains inconclusive with regards to both occupational and non-occupational exposure. However, given the acknowledged possibility of neurotoxic effects from high-level mercury exposure in general, more studies focusing on the assessment of possible neurotoxicity of mercury species originated from dental amalgam (but not limited to inorganic mercury) are needed, especially with regard to tremor and other neurological disorders such as Parkinson's disease.

Consistent with the current FDA 2018-2019 assessment, the FDA 2006/2009 white paper [7] concluded that "there is no evidence to support links between exposure to dental amalgam and systemic diseases that have been suggested to be causally related to dental amalgam mercury exposure, *e.g.,* …Parkinson's disease, Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis, autism, and peripheral neuropathies and tremors…. Recent prospective clinical studies [as of 2009] … have failed to demonstrate neurological or renal deficits in children who first received dental amalgam restorations at age six". The FDA 2010 review (Appendix 1) listed some neurological symptoms in relation to higher urinary/blood mercury levels among dental professionals. However, these symptoms were mostly

represented by the self-reported prevalence of psychosomatic symptoms, including memory loss, concentration difficulties, fatigue and sleep disturbances. The FDA 2010 literature review found no evidence of detrimental effect of amalgam-related mercury exposure on neurodevelopmental or psychosocial function of children aged 6-18 years; the evidence on possible links to autism/ASD among children came from a single study (*Geier et al 2009*, cross-referenced in the FDA 2018-2019 literature review), where dental amalgam related categorization (≥6 *vs*. ≤5 maternal amalgams) was possibly affected by confounding due to unmeasured factors. The FDA 2012 update (Appendix 2) further mentioned inconsistent reporting and controversies with regard to the autism-related diagnoses and classifications used in different studies; socio-economic status was found to be a strong confounding factor in a study that did not associate dental amalgam to early cognitive development.

Similar controversy regarding the dental amalgam attributed neurotoxicity was identified in the external LSRO 2004 report [5], which stated that "studies in the area of neuropsychological function were primarily negative or reported conflicting findings. Some raised concerns regarding experimental control of relevant confounding variables. In total, these studies failed to support the hypothesis that mercury vapor exposure, at the levels released by dental amalgam, interferes with human neuropsychological function or acts as an etiologic factor for the neurodegenerative diseases – Parkinson's disease and Alzheimer's disease". Similarly, the SCENIHR 2015 Report [i] stated that "several studies have explored the possible association of mercury derived from dental amalgam with a variety of adverse effects, particularly neurological and psychological or psychiatric diseases, including Alzheimer's disease, Parkinson's disease, and multiple sclerosis as well as kidney diseases"; however, "the causality evidence for such effects due to dental amalgam …[was found to be] weak because of contradictory reports and major challenges in exposure assessment". The SCENIHR 2015 Report [i] similarly stated that "the available data do not show a correlation between autism and blood mercury levels in small children", referring to "one paper [which] indicated an association between the severity of autism in autistic children and the number of dental amalgam fillings in their mothers during pregnancy". The SCENIHR 2015 Report [i] also concluded "Insufficient evidence was published to support or refute the hypothesis that Hg^0 exposure from dental amalgam interferes with human neuropsychological function or acts as an etiologic factor for the neurodegenerative diseases – Parkinson's disease and Alzheimer's disease. Mercury, however, does accumulate in the brain tissue of humans and animals exposed to Hg^0."

Due to known neurotoxic effects of mercury from accidental and some occupational (other than dentistry) types of exposure, potential neurotoxicity of mercury from dental amalgam has been addressed in numerous studies over time. However, no conclusive and reproducible evidence has been presented on potential links between dental amalgam and clinically detectable signs of neurotoxicity or neurodegenerative disease. Nonetheless, due to known neurotoxicity of mercury in general, there is an ongoing need for further assessment of potential neurotoxicity due to exposure to amalgam-related mercury, especially among dental professionals.

Pregnancy and Physical Development Related Outcomes

In a study on Egyptian female dental professionals, occupational exposure to mercury from dental amalgam was statistically associated with higher urinary mercury concentrations and more frequent spontaneous abortions and preeclampsia (RR=3.52; 95% CI: 1.29, 2.23 and RR=3.67; 95% CI: 1.25, 10.76, respectively; P<0.001), with the offspring being smaller for gestational age (RR=6.2, 95% CI: 2.3, 16.4; P<0.001). [63] However, no increased occurrence of congenital malformations or other pregnancy-related adverse outcomes (*e.g.,* low birth weight, preterm birth, small for gestational age, changed sex ratio, multiple birth, stillbirth, or prenatal death) was observed in a study on Norwegian female dental personnel compared to the general population. [142]

Among studies conducted on non-occupational mercury exposure, higher maternal and umbilical cord mercury levels were found in female subjects with amalgam fillings, but no significant differences were reported regarding newborns' weight, length, head circumference, sex ratio, or neonatal mortality in the group exposed to ≥3 amalgam fillings *vs*. non-exposed controls. [143] The number of maternal amalgams during pregnancy positively correlated with birthweight, with the girls born by mothers who had removed ≥1 amalgam fillings having an elevated risk for being small for gestational age (below the 10th percentile): adjusted OR=1.30 (95% CI: 1.02, 1.64; P=0.031).[144] The risk of stillbirth increased in mothers with multiple amalgam fillings, reaching OR of 1.93 (95% CI: 1.15, 3.23; P=0.003) in the group with ≥9 fillings; however, this trend did not remain statistically different after adjustment. The overall evidence was found by the study authors to be inconsistent for linking prenatal exposure to mercury from dental amalgam to adverse birth outcomes.

In a study on children randomized to dental treatment with amalgam or composites, no significant differences were reported regarding physical development (per 5-year changes in BMI-for-age z-scores,

body fat percentage, and height velocity). [145] However, girls with composite fillings had a lower likelihood of menarche during the 5-year follow-up, when compared to their counterparts with amalgam fillings (adjusted HR= 0.57; 95% CI: 0.35, 0.95; P=0.03).

Thus, there was no consistent evidence from the reviewed publications that would link adverse pregnancy- and physical development-related outcomes to mercury exposure due to maternal dental amalgam.

Similar to the current FDA 2018-2019 assessment, the following limitations were identified in previous internal and external assessments regarding perinatal/developmental outcomes and vulnerable populations. The FDA 2006/2009 white paper [7] stated that available studies "have not revealed any increased risks of adverse effects on reproductive health in women from exposure to dental amalgam. Limited information is available regarding long-term adverse health outcomes in specific populations, such as pregnant women or their offspring as a result of prenatal or postnatal (breast milk) exposures to dental amalgam mercury, in children less than six years old. …Recent prospective clinical studies, however, have failed to demonstrate neurological or renal deficits in children who first received dental amalgam restorations at age six." Although the FDA 2010 systematic literature review (Appendix 1) identified "a correlation between the number of maternal amalgam fillings and increased mercury in maternal blood, follicular fluid, and cord blood", none of the available studies were found to "provide conclusive evidence related to adverse health outcomes and exposure to dental amalgams"; "in the case of pregnancy and children under age 6, very little evidence …[was found to exist] regarding thresholds for concern or potential adverse outcomes". The FDA 2012 review update (Appendix 2) further confirmed that despite the "evidence in support of an [positive] association between the number of dental amalgams/surfaces in pregnant women and the Hg levels in the women and their developing fetuses or newborns", "no conclusions can be made regarding adverse health responses from dental amalgam mercury for women and their developing fetuses or newborns, children under six years of age, and women who are breastfeeding and nursing infants."

Among external reports, the LSRO 2004 report [5] stated that "the majority of the human reproductive and developmental literature [for dental amalgam] focused on exposure measures. Inorganic mercury in the placenta, maternal blood, and cord blood [were shown to] correlate with maternal dental amalgam load. Both methylmercury and inorganic mercury … [were shown to] be measured in breast milk", with

"the relative proportions of these species depend[ing] on the frequency of fish consumption, dental amalgam status, and occupational exposures". However, the LSRO 2004 report concluded that "insufficient evidence was published since the beginning of 1996 to support or refute the hypothesis that mercury exposure from dental amalgam restorations contributes to adverse pregnancy outcomes. Studies of human fertility suggest that occupational exposure to mercury vapor has little adverse effect on male fertility but may increase the prevalence of dysmenorrhea in females."

Although perinatal outcomes related to vulnerable populations such as pregnant women and their developing fetuses as well as neurodevelopmental outcomes in children have been the focus of many studies, no conclusive and reproducible evidence with regards to potential mercury toxicity due to exposure to maternal or personal dental amalgams was found throughout the reviews.

Cardiovascular Outcomes

In the study on occupational exposure among US dentists [76], urine mercury was associated with decreased systolic pressure (mostly among men), and hair mercury with increased diastolic pressure. In the study on occupational mercury exposure in relation to post-exercise heart rate recovery (HRR), all mean HRRs were lower in exposed *vs.* non-exposed subjects, allowing the authors to suggest that mercury exposure may affect cardiac autonomic functions. [146]

In the cohort study that examined risk of cardiovascular diseases [147], serum mercury was associated with both fish intake and number of amalgam fillings. HRs adjusted only for age showed inverse (protective) associations between serum mercury and total mortality or acute myocardial infarction. After adjustment for confounders including dental health, only the risk reduction for fatal acute myocardial infarction remained significant, while the likelihood of stroke increased with increasing serum mercury (HR=1.80; 95% CI: 1.11, 2.92 in the highest quartile).

A single case report described a male patient who developed metallic taste after having coronary artery stent implantation. [148] Rendering this case as the first evidence of possible galvanic interaction between patient's stent and amalgam fillings, the authors suggested amalgam replacement for patients who may have similar symptoms after stent implantation.

Thus, there was no consistent evidence from the reviewed publications that would link adverse cardiovascular outcomes to mercury exposure from dental amalgam.

Similar to the current FDA assessment, very little evidence was found in the previous assessments regarding cardiovascular outcomes in relation to dental amalgam. As stated in the FDA's 2015 response to Citizen Petitions on dental amalgam[o], "FDA believes the scientific studies implicating mercury exposure from dental amalgam and systemic diseases/conditions such as … idiopathic dilated cardiomyopathy (IDCM) are not sufficiently robust to draw definitive conclusions".
The external SCENIHR 2015 Report [i] referred to a study among Swedish women, stating that "no correlation of possible health symptoms for cardiovascular disease" (as well as diabetes, cancer, and early death) with the number of amalgam fillings was found.

Throughout the review assessments, the evidence on cardiovascular outcomes was very limited and not supportive in terms of their relevance to mercury from dental amalgam.

Renal Function and Other Subclinical Outcomes

In addition to the clinically-manifested outcomes discussed above, some studies investigated subclinical markers (other than mercury levels) as possible outcomes reflecting mercury exposure. Some studies associated dental amalgam exposure with minor changes in routine hematological or biochemical parameters such as hemoglobin [64], or cholesterol and aspartate/alanine aminotransferases [65].

Removal of amalgam restorations with subsequently reduced serum mercury was associated with significant changes in cytokine profile, indicating a decrease of Th1 proinflammatory markers [149]. In the study using a subset from the New England Children's Amalgam Trial [150], no overt immune alterations were associated with either amalgam or resin composite fillings; however, the B-cell responsiveness per CD23 and CD69 markers was reduced in children with amalgam *vs.* resin composite fillings. Exposure to amalgam fillings was also associated with decreased acetylcholinesterase activity [151].

[o] https://www.regulations.gov/document?D=FDA-2009-P-0610-0017

In the study assessing thyroid hormonal status among mother–child pairs [152], maternal total mercury was found to be a better predictor of the thyroid-stimulating hormone levels in children than their current total mercury. The presence of amalgam fillings was identified as the best predictor of maternal thyroxine and free thyroxine, which were lower among mothers with *vs.* without amalgam fillings. The number of maternal amalgam fillings inversely correlated with maternal free triiodothyronine levels. As a result, the low-level prenatal and early postnatal mercury exposure was suggested to affect the thyroid function in offspring.

Several studies examined possible associations between dental amalgam exposure and renal function biomarkers. One study identified urine N-acetyl-β-D-glucosaminidase as the most sensitive marker, indicating that low-level exposure to mercury from amalgam fillings may affect renal tubular function in children. [10] However, no associations between the levels of N-acetyl-β-D-glucosaminidase (and two other markers) and the presence of amalgam or resin composite restorations were found in the study investigating renal function among the New England Children's Amalgam Trial participants [153]. In other US studies [154, 155], which employed a supposedly more sensitive analysis of the subset from Casa Pia Dental Amalgam Clinical Trial (Portugal), significant dose-dependent correlations were found between cumulative exposure to amalgam-related mercury and porphyrins associated with mercury bioburden (pentacarboxyporphyrin, precoproporphyrin, and coproporphyrin). A significant dose-dependent correlation was observed for glutathione-S-transferase-α that is more indicative of kidney damage in the *proximal* tubules where mercury is expected to accumulate, but not for glutathione-S-transferase-π that is indicative of the damage in *distal* tubules [155].

Several studies addressed subclinical markers pertaining to oxidative stress and the antioxidant system. In one study, non-occupational exposure to dental amalgam was associated with *increased* plasma levels of superoxide dismutase-1 and glutathione (reduced form); based on its strong correlation with mercury levels, superoxide dismutase-1 was suggested as a candidate biomarker for assessing chronic mercury toxicity.[156] However, in a study on occupational exposure [67], superoxide dismutase (as well as glutathione peroxidase) activity in blood was significantly *decreased*, negatively correlating with duration of work among dental staff. In the study that investigated selenium-related anti-oxidant defense among chlor-alkali plant workers, the number of amalgam fillings was shown to correlate with urine mercury which, in its turn, inversely correlated with expression of thioredoxin reductase-1. [66]

Among a few reviewed studies that explored mercury exposure in relation to genotoxicity in *ex vivo* samples[p], no significant signs of genotoxic damage due to dental amalgam was reported [157, 158]. However, patients who had dental amalgams (along with metal-porcelain fixed crowns) showed higher levels of condensed chromatin along with elevated mercury [157]. In one study, no significant DNA damage was found by comet assay, while the micronucleus test showed genotoxic damage in relation to both amalgam and resin composite fillings. [159]

Thus, despite a relatively high number of publications with the clinically-derived evidence on different subclinical outcomes, the existing evidence on biochemical and other lab test based changes is insufficient to support their use as prognosticators and/or indicators of clinically-manifested adverse health outcomes attributed to mercury from dental amalgam.

Similar to the current findings in FDA 2018-2019 review, the previously identified studies on potential nephrotoxicity of mercury from dental amalgam were focused on subclinical outcomes such as kidney function markers and mercury measurements in kidney tissues. The 2006/2009 FDA White Paper [7] stated that "limited information is available regarding long-term adverse health outcomes in specific populations, such…persons with … renal dysfunction. Recent prospective clinical studies, however, have failed to demonstrate … renal deficits in children who first received dental amalgam restorations at age six." The FDA 2010 systematic literature review (Appendix 1) referred to the evidence demonstrating that mercury levels measured in the kidney cortex among kidney donors increased with total number of amalgam fillings (by 6% with every additional amalgam surface). The FDA 2010 review also mentioned "incipient increases in urine concentrations of porphyrins [which] may be indicative of mercury exposure" as well as "microalbuminuria [which] was associated with amalgam at ages 3-5 years"; the review concluded, however, that "the implications of these findings … [remained] unclear from the studies reviewed". Addressing the studies using urinary porphyrin patterns as putative surrogate markers of mercury toxicity, the FDA 2010 review mentioned that the mean concentrations of hexacarboxyl, pentacarboxyl-, and copro-porphyrins were reported to be elevated among autistic vs. neurotypical children, especially boys (aged 2-12 years). However, due to a number of significant limitations such as small sample sizes, no validation of other sources of mercury exposure, no

[p] Note: the current review is limited to clinically-derived evidence and therefore does not include *in vitro* or animal studies on genotoxicity.

unaffected comparison groups, the FDA 2010 review found no reliable evidence of detrimental effects of amalgam-related mercury on the kidney function among children aged 6-18 years. The FDA 2012 review update (Appendix 2) included studies that reported positive correlations between the number of maternal amalgam fillings and fetal or infants' renal mercury; maternal amalgam fillings were also associated with some renal and oxidative stress markers (*Al-Saleh 2012*, referenced in the current FDA 2018-2019 review). However, FDA determined that the results of this one study were inconclusive as the authors could not discount that the increase in a urinary biomarker for kidney function was not exclusively due to Hg exposure from dental amalgam, and that exposure to other mercury sources might have also contributed to the body's total mercury burden; therefore, a causal association between Hg from amalgam exposure and the adverse outcome could not be concluded. Among other subclinical health outcomes, the FDA 2012 review update referred to limited evidence on the associations between maternal blood Hg levels and thyroid-stimulating hormone (*Palkovicova et al 2008*; cross-referenced in the current FDA 2018-2019 review).

Among external reports, the PHS 1993 Report [1] stated that “in low-level occupational exposures, the subclinical effects detected have occurred in groups with mean tissue mercury levels that are only tenfold higher (internal note: the original text sounds confusing) than those of the general population; however, the relationship between the observed effects and tissue levels is unclear.” The SCENIHR 2015 Report [i] stated that “parameters of kidney function may be influenced by mercury from amalgam, but there is no convincing evidence that dental amalgam is associated with a clinically decreased kidney function (decreased renal clearance) in the patients in the short or long term. On the other hand, decreased kidney function (decreased renal clearance) is likely to decrease the ability to eliminate mercury and other substances via the urine”. The LSRO 2004 report stated that there was no “sufficient information to support the hypothesis that mercury exposure at doses absorbed from dental amalgam restorations cause adverse effects on renal function”, although some findings suggested that “[occupational mercury] workers are generally exposed to substantially higher mercury vapor levels than individuals with dental amalgam restorations.”

Due to known nephrotoxic effects of mercury, potential nephrotoxicity in relation to dental amalgam was addressed in numerous studies throughout the assessment periods. However, no conclusive and reproducible evidence was presented on potential links between dental amalgam and clinically detectable signs of nephrotoxicity, including subclinical markers of renal function. The available data on

additional subclinical (including non-renal) markers tested throughout the assessment periods was found to be limited for drawing any definitive conclusions. However, due to known nephrotoxicity of mercury in general, there is an ongoing need for further assessment of potential nephrotoxicity due to exposure to amalgam-related mercury as well as discovery of its putative predictors and modifiers.

Putative Effect Modifiers of Amalgam-related Mercury Toxicity

In addition to clinical and subclinical outcomes resulting from mercury exposure, many studies explored variables that may act as possible effect modifiers, thus causing heterogeneity and interindividual variability in the outcomes representing mercury toxicity. As detailed below, the effect modification was attributed to various genetic and non-genetic factors that were shown to affect mercury levels as well as other amalgam-related outcomes. Further, dental amalgam *per se* exerted possible modifying effects on other diagnostic and therapeutic procedures: the presence of amalgam fillings affected, for instance, the *Helicobacter pylori* frequency and eradication treatments. [160]

Genetic Markers with Possible Modifying Effects on Mercury Toxicity

Many studies investigated genetic markers represented by single nucleotide polymorphisms (SNP) and other changes in genes that are known to be involved in mercury kinetics and toxicity and therefore are likely to modify biological responses and health outcomes related to mercury exposure.

In a series of studies examining genetic markers in relation to mercury levels in dental professionals[69, 74, 75], some polymorphisms in the glutathione s-transferase and selenoprotein genes implicated in mercury metabolism were associated with urine mercury (GSTT1 deletion), hair mercury (GSTP1-105, GSTP1-114, GSS 5'), or both (SEPP1 3'UTR). [75] No significant relationships were found between urine mercury levels and DNA methylation assessed for some genes related to epigenetic processes (DNMT1) and protection against mercury toxicity (SEPW1, SEPP1).[74] In the co-authored study [161] on 88 SNPs in the genes relevant to mercury toxicokinetics and glutathione metabolism and involving selenoproteins, metallothioneins and xenobiotic transporters, possible effects on mercury bioburden among dental professionals were suggested for 6 SNPs residing in GCLC, MT1M, MT4, ATP7B, and BDNF.

In the study examining 13 metallothionein-related SNPs among dental professionals [162], some MT1M_rs2270837 and MT2A_rs10636 genotypes were associated with lower *urine* mercury levels, and

some MT1M_rs9936741 and MT1A_rs8052394 genotypes with lower *hair* mercury levels. Neurobehavioral changes among dental professionals were associated with the additive effect of urinary mercury and a polymorphism in serotonin transporter gene-linked polymorphic region (5-HTTLPR). [163] However, no consistent evidence in relation to mercury levels and peripheral nerve function among dental professionals was found in the larger study investigating a possible biomarker role for 26 SNPs and 2 deletion polymorphisms in genes coding glutathione-related proteins, selenoproteins, and metallothioneins [164].

Several studies used the Casa Pia Dental Amalgam Clinical Trial subsets to investigate candidate SNP biomarkers in the genes that were previously suggested to modify mercury toxicity and/or neurobehavioral function in adults. [165-168] Sex-dependent modification of mercury-related neurobehavioral effects in children was suggested for SNPs in coproporphyrinogen oxidase CPOX4 [165], catechol-O-methyltransferase COMT [167], and metallothioneins (MT1M_rs2270837 and MT2A_rs10636) [168]. In a summary of the findings on putative genetic modifiers of mercury neurotoxicity in children (per genotyping for a total of 27 variants in 13 genes), the broadest range of effects was attributed to CPOX4_rs1131857. [166]

Thus, some SNPs (*e.g.,* metallothionein-related MT1M_rs2270837 and MT2A_rs10636) were repeatedly suggested as putative effect modifiers in occupational and non-occupational exposure to dental amalgam. However, authors report that the currently available biomarker studies were limited to discovery phase and, as a result, none of the discussed biomarkers was rendered ready to enter clinical practice as a reliable indicator of interindividual variability and a predictor of enhanced susceptibility to the dental amalgam related mercury toxicity. [165-168]

The FDA 2006/2009 White Paper and Addendum [7] states, "specific polymorphisms for enzymes that decrease glutathione (GSH) availability were reported to effect a decreased metabolism of inorganic mercury resulting in increased tissue and urine levels, theoretically rendering individuals with such polymorphisms more susceptible to mercury toxicity. …Likewise, apolipoprotein-E genotyping has been investigated as a possible indicator of susceptibility to heavy metal neurotoxicity but data …[were] inconclusive". The FDA 2010 review identified some evidence on "genetic factors that potentially increase human susceptibility to mercury toxicity; however, all of the genetic[s]-related results were

from the same study cohort"; "an additive effect of urinary mercury and 5-HTTLPR polymorphism on specific behavioral domains" among dental professionals was mentioned as a finding of interest. Among external reports, the LSRO 2004 Report [5] stated that "while there is evidence that a small portion of the human population demonstrates this allergic sensitivity, there is insufficient evidence for other types of sensitivity, such as genetic susceptibility". As further assessed in the SCENIHR 2015 Report [i] "the studies presented …seem to indicate that genetic variation may have an influence also on responses to mercury-induced toxicity. In this case, calculated exposure limits will protect the average subject, but may be insufficient to protect those with genetic polymorphism to relevant enzymes involved in the toxicodynamics of mercury. However, no prospective clinical studies clearly showing the influence of genetic variations on the occurrence of adverse effects due to mercury from dental amalgam are available. Therefore, especially in this area further research is needed before clinical conclusions could be drawn".

Thus, despite the well-recognized role of potential genetic biomarkers for predicting and/or diagnosing mercury toxicity as well as a relative abundance of studies aimed at discovery of mercury-related biomarkers, the reliability of available biomarker data is affected by methodological limitations and the existing evidence on candidate biomarkers is not sufficient for their implementation in clinical setting.

Sex as Possible Effect Modifier in Mercury Toxicity

Sex was suggested to modify mercury levels and other outcomes associated with dental amalgams in numerous studies on both occupational and non-occupational exposure.

Higher mercury concentrations among male dental staff were reported in the 35-year review of the mercury monitoring service for Scottish dental practices [68]. Higher hair, blood, and urine mercury levels in the male dental workers were also reported in the US. [69] A significant association between urine mercury and systolic pressure decrease among the US dentists was driven mostly by males [76]. Cumulative mercury exposure was shown to be higher among male US dentists in the study [59], which did not exclude possible risk of multiple sclerosis and tremor in relation to occupational mercury exposure.

On the other hand, as discussed in some studies on non-occupational exposure, women may have longer half-life of mercury retention in kidneys and therefore lower elimination rate compared to men [13]. Consistent with that finding, a study investigating dental amalgam mercury exposure in a pediatric

population[32] showed significantly higher urine mercury levels in girls compared to boys. Based on a significant inverse relationship between the age and urinary mercury levels, some authors suggested that younger populations exposed to mercury may experience more mercury-associated adverse effects [35]; this age-related trend was further influenced by the sex-related differences, with girls having significantly higher urinary mercury levels than boys.

In contrast to the above findings, a study which suggested the combined role of sex and BMI as the major modifying effect in dental amalgam exposure, urine mercury levels were estimated to be higher in men *vs.* women [15]. In a study that suggested modifying effects by both sex and age [20], blood mercury levels were similar for younger men and women (<40 years), but slightly higher among women *vs*. men in the older group (40–65 years). Two Canadian studies [21, 28] showed higher urinary mercury levels in women *vs.* men; the difference between sexes was shown to increase with age in the nationally representative study [21].

Among the studies on outcomes other than mercury levels, exposure to mercury from amalgam fillings was associated with a relatively higher risk trend for Alzheimer's disease among women *vs.* men: OR=1.132 (95 % CI: 1.022, 1.254) *vs.* 1.07 (95 % CI: 0.962, 1.196), respectively. [31] Positive patch tests to dental materials, including amalgam, were found more frequently among women *vs*. men. [101] Possible sexual dimorphism among developmental outcomes in relation to maternal amalgam mercury exposure was suggested by the slightly elevated risk of being small for gestational age among girls [144] and a few subtle sex-dependent trends in some neurodevelopmental outcomes.[139] Sex-related trends were also identified in relation to putative genetic markers of mercury toxicity. A male sex-specific trend of SEPP1 hypomethylation with increasing hair mercury levels was attributed to methylmercury exposure.[74] In several studies [165-168], modification of mercury effects on neurobehavioral outcomes (which was associated with a number of variants in CPOX, MT1M, MT2A, COMT, and to a lesser degree – in TDO2, GRIN2A, GRIN2B, BDNF, GSTT1, SLC6A4, KIBRA, and SEPP1) was mostly limited to boys and was referred to as the first evidence demonstrating sexual dimorphism and genetic susceptibility to adverse neurobehavioral effects of mercury exposure in children.

Thus, sex (alone or in combination with age or BMI) was identified as a major demographic factor capable of modifying dental amalgam-related mercury toxicity; however, the identified sex-related trends in relation to mercury levels and other possible outcomes were not consistent.

Similar to the current FDA 2018-2019 assessment, the FDA 2015 response to Citizen Petitions on dental amalgam[q] stated that "the available data … are limited and inadequate to reliably quantify gender [sex]-related differences in toxicity".

Country/Residence Area and Ethnicity as Possible Effect Modifiers in Mercury Toxicity

Some studies suggested modifying effects due to geographic location as well as race/ethnicity-related factors representing genetic background and/or diet and cultural traditions.

In an international study among women from European and non-European countries, country and/or city were important determinants explaining 26% of the variance for blood mercury levels [23]. In the Czech study [34], mercury values in mothers (but not in children) were significantly higher in urban than in rural populations. Cord blood mercury levels were associated with different thyroid hormone changes in children of Slovak/Caucasian *vs.* Roma origin [152]; however, these variations may have been due to different frequencies of amalgam fillings among mothers from these ethnic groups. As mentioned in the 2010 review, higher levels of hair (but not urine) mercury were reported among children with self-identified *other* (not black, white, or Hispanic) race; this trend, however, was attributed to ethnic differences in fish consumption and not to amalgam fillings. [4]

US dentists of Asian origin were reported to have higher hair and blood mercury levels compared with their counterparts of other races, which was also attributed to traditionally higher fish consumption. [69] Similarly, higher blood mercury levels were reported in patients of Asian or other/mixed origin compared to self-identified Caucasians in the Canadian population.[22] Among the newcomer population in Vancouver (Canada), blood mercury levels were higher among East-Asian *vs.* South-Asian women, with dental amalgams identified as one of the main exposure sources along with seafood and traditional remedies.[17]

In addition to conventional factors such as seafood consumption, mercury levels were suggested to be modified by education, smoking, and alcohol [20, 22, 24, 34, 36] as well as by chewing gum or grinding teeth.[37, 134] As suggested by the trends pertaining to cardiovascular disease risk [147], mercury

[q] https://www.regulations.gov/document?D=FDA-2009-P-0610-0017

exposure from different sources may involve complex and even opposing effects implicating the factors other than mercury (*e.g.,* polyunsaturated fatty acids from fish consumption). In some rare cases, modifying effects were presented by unconventional factors such as foreign birth of mother, or use of special products reflecting different cultural, religious, and ethnicity-related traditions.[17, 46]

Possible modifying effects of demographic factors (other than sex) in relation to variations in dental amalgam exposure and potential mercury toxicity have not been addressed in previous assessments; however, other modifying effects such as gum chewing were mentioned in the current (2018-2019) and previous (2010) FDA reviews. As further assessed in the LSRO 2004 report, "several behaviors and/or other factors have been proposed to modulate mercury exposure from dental amalgam. These include chronic gum chewing, bruxism, alcohol consumption, and the placement and removal of dental amalgam restorations".

Studies Assessing Dental Amalgam Safety at Populational Levels

In the single identified trend analysis [169] pertaining to mercury exposure from dental amalgams in the US population, the least conservative scenario predicting the lowest levels of exposure suggested that 67.2 million Americans may exceed the reference exposure level of 0.3 µg/m^3 for inhalation of elemental mercury vapor as established by the US EPA. The same authors (SNC-Lavalin Environment group & GM. Richardson, Ottawa, Ontario) also released a report (2010)[r] arguing that "a large proportion (1/3rd) of the US population is concurrently exposed to elemental mercury vapor (Hg^0), methylmercury (MeHg), and lead (Pb) on a daily basis" and that population health risks from these chemicals should be assessed not on an independent basis (which is a routine practice now), but for *concurrent* exposures and *joint* toxicity, due to their common ability to cross the blood-brain and placental barriers and cause additive neurotoxic effects. For Hg^0, 101.5 million Americans were suggested to exceed the urine Hg concentration per the cited reference exposure level of 0.06 ug/m^3 developed in Canada. For methylmercury, 1.8 million Americans were suggested to exceed the Canadian reference blood level of 8 ug/L established in relation to fetal neurodevelopmental effects. However, these results were mostly derived from model-based calculations [169] and therefore were subject to interpretation bias. In the meantime, the US or Canadian studies based on actual mercury

[r] Mercury Exposure and Risks from Dental Amalgam, Part 2: Cumulative Risk Assessment and Joint Toxicity: Mercury Vapour, Methyl Mercury and Lead; prepared by SNC-Lavalin Environment, Ottawa, Ontario and submitted to International Academy of Oral Medicine and Toxicology (November 11, 2010).

measurements among large study populations did not confirm high and widespread mercury levels or other tangible adverse health effects due to exposure to mercury from dental amalgam (among bearers or occupational).

In the Canadian study [15], amalgam fillings were deemed as a non-negligible and unnecessary source of mercury exposure. However, referring to the Health Canada's 1996 Position Statement on Dental Amalgam[s] and acknowledging that dental amalgam remains in use until evidence of harmful health effects is produced (as opposed to the precautionary approach applied in some European countries, *i.e.,* not used until evidence of safety is produced), the authors stated that there was insufficient evidence to support a total ban on dental amalgam or recommend removal of intact amalgam fillings in cases with no adverse effects attributable to mercury exposure. The recommended avoidance of amalgam fillings was limited to primary teeth in children as well as to pregnant women and individuals with kidney disease.

Similarly, use of safer dental materials was recommended to avoid possible risk from unnecessary exposure to dental amalgam [28]; however, urine mercury levels reported in this Canadian study were considered too low to pose health risks. In addition to the referenced level per Health Canada (Hg^0 of 0.011 µg/kg-day), the authors referred to the thresholds per Human Biomonitoring Commission of the German Federal Environment Agency, *i.e.,* 5 µg Hg/g-creatinine in urine as the safety level below which there is no risk for adverse health effects and therefore no need for action as well as 20 µg/g-creatinine in urine as the concentration above which there is an increased risk for adverse health effects and, consequently, an urgent need to reduce exposure and provide biomedical care.

Overall, evidence from the US studies (as discussed in the Summary sections above) showed that urine and hair mercury concentrations at the levels considered to be hazardous were rare [74] and the dental amalgam attributable mercury levels were mostly described as corresponding to the US NHANES survey estimates [76]. In a study that is self-described as the first study conducted on a nationally representative US population [24], average blood mercury levels were below the referenced safety thresholds established by the WHO and the US EPA. However, despite the demonstrated relationship between dental fillings and blood mercury levels, interpretability and usability of the results [24] in

[s] Health Canada: The Safety of Dental Amalgam. Health Canada: Ottawa; 1996.

reference to the US general population are restricted by major caveats such as the lack of information on the types of restoration materials and the study design precluding definitive evaluation of causality.

Regarding occupational exposure among US dentists, a large study recruited via the American Dental Association [59] clearly demonstrated a drastic decrease in urinary mercury concentrations (by 90% throughout the screening program spanning from 1976 to 2012), which was attributed to heightened hygiene awareness, development of pre-capsulated amalgam, and increased use of composite resins.

The European Union published a report by the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR [i]) in 2015 that concluded dental amalgam does not pose a health risk for the *general* population, and the currently available evidence neither precludes the use of amalgam in dental restorations nor suggests that pre-existing amalgam restorations should be removed as a preventive measure. Additionally, SCENIHR recommends that the choice of material should be based on individual patient characteristics such as primary or permanent teeth, pregnancy, and the presence of impaired renal clearance or allergy to mercury. Although the incidence of adverse health effects due to occupational and non-occupational exposure to dental amalgam mercury appeared to be in the same order of magnitude, dental personnel were suggested to be at greater risk than the general population, as evidenced by the difference in urine mercury levels referenced as 0.1-5 µg/L in non-occupational groups *vs.* 3-22 µg/L in dental personnel. Stating that dental amalgam restorations are currently considered the main source of inorganic mercury exposure (per urinary excretion), the SCENIHR 2015 Report [i] recognized the need for further research particularly evaluating potential neurotoxicity of amalgam-derived mercury as well as genetic modifying effects that might enhance individual susceptibility to mercury toxicities.

Evidence Critique and Assessment

In this section we discuss the main limitations of reviewed studies and summarize the main findings stratified by overall risk trends pertaining to populations with occupational and non-occupational mercury/amalgam exposure (*e.g.,* dental professionals, pediatric and adult patients), various outcomes of interest (*e.g.,* elevated mercury levels, oral mucosa lesions), and potential effect modifiers (*e.g.,* sex, genetic polymorphisms).

Despite the sizeable amount of retrieved data, several limitations impacted overall analysis and interpretation and, as a result, limited comprehensive conclusions on mercury-related toxicity due to occupational and non-occupational exposure to dental amalgam mercury.

In some publications, data quality and/or generalizability were limited by small sample sizes (*e.g.,* a total of 10 subjects [170]), or unconventional study locations, such as the proximity of military conflicts (*e.g.,* Baghdad, Iraq) [65]); environmental pollution zones (*e.g.,* the mining area in Mexico [16]*;* the waste-to-energy incinerator in Turin, Italy [14]). Generalizability of some evidence was also affected by unconventional non-occupational exposure sources (*e.g.,* use of elemental mercury in traditional rituals and folk medicine remedies [46]; or use of mercury-containing cosmetic products [71]), or by occupational practices reflecting poor professional hygiene (*e.g.,* dental wastewater with mercury levels beyond permissible limits [73]).

Conclusions derived from some studies were of limited utility owing to a single data source and the lack of supporting evidence from other independent clinical studies (*e.g.,* an accelerated mercury release from dental amalgams in response to ionizing/ non-ionizing radiation was suggested in the single clinical study [171] that cited experimental studies from the same Iranian Shiraz University of Medical Sciences)[t]. Furthermore, the quality of overall evidence was affected by general cross-cutting limitations, as discussed in the next section.

Discussion of Overall Findings

Findings from the Main Review of the Literature Published between 2010 and Sep 2018

Although the metallic, elemental mercury used in dental amalgam is associated with a well-established toxicological risk and the reduction of mercury in the human environment would be beneficial, there is insufficient evidence to support that exposure to mercury from dental amalgam causes adverse health effects in the general population or in vulnerable populations. The current evidence regarding amalgam-related health effects (other than increased mercury levels), includes limited reports of clinical manifestations such as tremor or other neurological conditions potentially associated with mercury from

[t] Note, in addition to the single clinical study described here, additional recently published preclinical studies on this subject are identified in the Addendum to this review.

dental amalgam, but the causality of these effects is challenging to interpret due to inconsistency of the findings. No increased risks of adverse *systemic* effects have been clearly established in the general population or among dental professionals. *Local* adverse effects (*e.g.,* lichenoid/allergic mucosal lesions) are usually managed by the removal of amalgam fillings, which, however, does not always result in complete healing.

Some reports of atypical reactions attributed to mercury indicate possible individual susceptibility, the underlying reasons of which are poorly understood. Despite the reasonable assumption that gene polymorphisms affecting mercury kinetics and excretion may influence individual susceptibility to mercury exposure and modify the resultant toxicity in different population segments, the existing evidence on candidate biomarkers is not sufficient to support their use in clinical practices or regulatory considerations.

Importantly, the current evaluation of causality and modifying effects is complicated by the likely inaccuracies in the assessment of dental amalgam exposure because it is often based on mercury content in biofluids (mainly urine). An accurate assessment of the dental amalgam derived mercury is complicated by recent data indicating possible *in vivo* cross-transformation of elemental mercury and methylmercury driven by gastrointestinal microbiota. As a result, a large part of the mercury excreted via urine may have dietary (organic) origin and therefore urinary mercury may not be a precise indicator of inorganic mercury, especially at a low-level amalgam exposure. The recent evidence also challenges the conventional assumption that hair mercury levels are not impacted by the mercury released from amalgam fillings. However, no currently available alternatives have been identified as non-invasive and reliable markers for the accurate evaluation of mercury exposure sources, which is imperative for drawing any unequivocal conclusions on the causality between dental amalgam and adverse health effects.

Further attention is recommended for evaluating possible additive effects of unconventional exposure sources, *e.g.,* use of elemental mercury in folk medicines and remedies and other special products, especially among pregnant women and breastfed infants.

The strength of currently available evidence regarding the safety of dental amalgam is dependent on proper identification of the source (dental amalgam *vs*. diet) of the species of mercury. As a result, there is a need for updated methodological approaches and study designs that would precisely differentiate between organic and inorganic mercury forms, thus allowing an accurate identification of their possible sources. An updated causality analysis using novel mercury exposure indicators and predictors is needed to determine whether well-documented mercury increases in body fluids may lead to detectable (clinical or subclinical) manifestations that would constitute definitive health risk due to dental amalgam.

Based on the most recent comprehensive review of clinical studies published since 2010, there was no new evidence that substantially changes our understanding of clinically detectable adverse health outcomes related to dental amalgam mercury exposure. This is consistent with previous analyses conducted by DHHS and FDA. Notably, there are uncertainties regarding the currently available evidence due to the recently identified technical limitations of mercury and methylmercury measurements.

In summary, there was a continuity in the overall assessment of potential risks attributable to mercury from dental amalgam, from the PHS 1993 Report [1] which concluded that "available data are not sufficient to indicate that health hazards can be identified in non-occupationally exposed persons" to the FDA's final rule on dental amalgam (74 FR 38691) [6] stating that "in light of the evidence from air monitoring, biological monitoring, and clinical studies, FDA concludes that exposures to mercury vapor from dental amalgam is not associated with adverse health effects in the population age six and older."

At the same time, the evidence gleaned throughout the reviews was found insufficient to dismiss any potential concerns in relation to dental amalgam, starting from the PHS 1993 Report's [1] statement that "health hazards …cannot be dismissed" to the current FDA 2018-2019 assessment which acknowledged the elevated mercury levels, especially among dental professionals, as a mercury-related adverse outcome most attributable to dental amalgam. As further assessed in the SCENIHR 2015 Report [i] "the causality evidence for such effects [neurological, psychological or psychiatric diseases, including Alzheimer's disease, Parkinson's disease, and multiple sclerosis as well as kidney diseases] due to dental amalgam is weak because of contradictory reports and major challenges in exposure assessment, which

is generally expressed as total mercury in body fluids (mainly urine), without differentiating between organic *vs*. inorganic forms as well as between sources (dietary *vs.* dental amalgam or others)".

Concerns regarding the lack of mercury speciation analysis in the available studies were consistently voiced in the initial FDA 2010 review. As identified in the current FDA 2018-2019 review, the recent evidence on possible *in vivo* methylation/demethylation of mercury species elevates the need to derive an adequate mercury measurement methodology that enables accurate determination of mercury/methylmercury exposure sources (dental amalgam *vs.* diet) as a prerequisite for proper assessment of potential toxicity unequivocally attributable to the mercury from dental amalgam.

Cross-Cutting Study Limitations and Identified Knowledge Gaps

Possible inaccuracies in mercury measurements and subsequent misattribution of mercury exposure sources can be pointed out as the major cross-cutting limitations pertaining to mercury levels in the body as the main outcome used for assessment of both occupational and non-occupational exposure.

First, interpretability of the amalgam-attributed mercury levels was limited by the lack of details on amalgam-specific exposure, with the available information routinely limited to the number of teeth (surfaces) with amalgam fillings, or even to their absence or presence with no other quantitative assessment. However, a more accurate assessment of amalgam-related mercury exposure may require taking into account the amount of time since each amalgam restoration was placed in the mouth.[u,] [37] Comprehensive interpretation of dental amalgam exposure should also take into account habits, which may increase mercury release from dental amalgams, *e.g.,* chewing gum, or grinding teeth (bruxism). [37, 134] Some studies were prone to possible measurement errors due to incorporating the datasets spanning over several decades [59, 70] and/or based on different measurement methods for the same type of biospecimens. [116]

Some authors posit that a majority of inhaled mercury vapor is eliminated via feces [35], with urinary mercury excretion representing a minor excretory pathway.[v] However, none of the reviewed records

[u] Maserejian, N.N., Trachtenberg, F.T., Assmann, S.F., Barregard, L., 2008. Dental amalgam exposure and urinary mercury levels in children: the New England children's amalgam trial. Environ. Health Perspect. 166, 256–262.
[v] Clarkson TW, Nordberg GF, and Sager PR. Reproductive and developmental toxicity of metals. Scand J Work Environ Health 1985; 11: 145–154.

assessed fecal mercury, and the mercury assessment in almost all relevant studies was limited to mercury measurements in the blood, urine, or hair.

Urine and hair mercury levels have been historically accepted as proxy estimates for inorganic (amalgam-derived) mercury and organic (fish-derived) methylmercury, respectively. [69, 74-76, 116]. However, as indicated by positive correlation between amalgam fillings and methylmercury in maternal and cord blood [152], dental amalgam mercury exposure may not be limited to inorganic mercury and may result in the formation of methylmercury due to potential methylation of inorganic mercury by host's microflora, as suggested by the cited *in vitro* evidence[w].

According to some authors [128], elemental mercury (Hg^0) from dental amalgam may convert in the gut to methylmercury, which has a higher entry rate to cross the blood-brain barrier than inorganic mercury (Hg^+ and Hg^{2+}) and therefore may be a more likely candidate for explaining the increased risk for Parkinson's disease attributed to dental amalgam fillings.

Furthermore, conventionally accepted reliability of the urine mercury concentration as a specific indicator of exposure to elemental/inorganic mercury was questioned in the study assessing mercury stable isotopes.[172] High positive $\Delta^{199}Hg$ values were found in the hair from dental professionals, confirming an association between fish consumption and hair mercury concentrations which are expected to reflect exposure to the fish-derived methylmercury. In contrast, urine from the same individuals was characterized by a range of $\Delta^{199}Hg$ values significantly correlating with the number of personal dental amalgams. Based on possible demethylation of methylmercury within the body, urine mercury was suggested to represent a mixture of dietary methylmercury and amalgam-derived inorganic mercury, and >70% of urine mercury among individuals with up to 10 amalgam fillings was estimated to come from the dietary methylmercury. As a result, urine mercury (which is the most frequently used biomarker for inorganic mercury) was suggested to overestimate exposure from dental

[w] Heintze U, Edwardsson S, Derand T, Birkhed D (1983) Methylation of mercury from dental amalgam and mercuric chloride by oral streptococci in vitro. Scand J Dent Res 91:150–152.
Liang L, Brooks RJ (1995) Mercury reactions in the human mouth with dental amalgams. Water Air Soil Pollut 80:103–107.
Yannai S, Berdicevsky I, Duek L (1991) Transformations of inorganic mercury by Candida albicans and Saccharomyces cerevisiae. Appl Environ Microbiol 57:245–247.

amalgams. Furthermore, the inorganic mercury from dental amalgam was shown to contribute to hair mercury[x], thus questioning the reliability of hair mercury as a conventional biomarker for organic methylmercury. Consistent with that, exposure to dental amalgam was associated with increased hair mercury concentrations in several reviewed studies. [18, 39, 52, 68, 173, 174] Taken together with the emerging evidence on possible methylation of mercury and demethylation of methylmercury by intestinal microbiota,[y] these data strongly suggest that conventional methodology for mercury measurements in relation to different exposure sources (dental amalgam *vs.* seafood) may be compromised by possible *in vivo* cross-transformation of Hg / MeHg and the resultant inaccuracies in their assessment.

Thus, limitations related to urine and hair concentrations that have been used as indicators of inorganic mercury and organic methylmercury, respectively, likely affected, to some extent, all studies assessing the causality in relation to dental amalgam *vs*. fish consumption as two predominant sources of exposure. As a result, the recent evidence suggests that consumption of foods (e.g., fish) contaminated by mercury may contribute to the mercury bioburden that has been conventionally attributed to dental amalgam and *vice versa*, dental amalgam may contribute to the mercury bioburden that has been conventionally attributed to diet.

[x] Manceau A, Enescu M, Simionovici A, Lanson M, Gonzalez-Rey M, Rovezzi M, Tucoulou R, Glatzel P, Nagy KL, Bourdineaud JP. Chemical Forms of Mercury in Human Hair Reveal Sources of Exposure. Environ Sci Technol. 2016 Oct 4;50(19):10721-10729. DOI: 10.1021/acs.est.6b03468 Epub 2016 Sep 22.

[y] Uchikawa T, Kanno T, Maruyama I, Mori N, Yasutake A, Ishii Y, Yamada H. Demethylation of methylmercury and the enhanced production of formaldehyde in mouse liver. J Toxicol Sci. 2016;41(4):479-87. doi: 10.2131/jts.41.479.
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Martín-Doimeadios RC, Mateo R, Jiménez-Moreno M. Is gastrointestinal microbiota relevant for endogenous mercury methylation in terrestrial animals? Environ Res. 2017 Jan;152:454-461. doi: 10.1016/j.envres.2016.06.018. Epub 2016 Jun 16.

Addendum: Update to Main Review of the Literature Published between Sep 2018 and Aug 2019

This addendum is aimed to incorporate the relevant publications published since the end of the main review (*i.e.,* Sep 24, 2018) and therefore is based on the queries replicating the initial search strategy (as described in the main review's Methods section and Figure 1) but limited to the timeframe of Sep 2018 – Aug 2019. As of Aug 12, 2019, the searches of PubMed and EMBASE databases using the initial search strings resulted in 19 and 136 records, respectively. After combining the results in EndNote and removing replicate findings from different searches, a total of 145 records constituted the pool for the 1st pass (*i.e.,* abstract-based) review. Using exclusion/inclusion criteria similar to the main review, the addendum's 1st pass review aimed to include original studies assessing adverse outcomes in relation to dental amalgam, while further excluding replicate findings as well as records representing non-original research (*e.g.,* meta-analyses, expert opinions, *etc.*) or research not related to the review's subject (*e.g.,* outcomes evaluating effectiveness and not safety). A total of 42 records were selected for the 2nd pass (*i.e.,* full-text based) review, which identified 20 publications qualifying for the update of the main review.

Almost all of the addendum's publications addressed non-occupational exposure (18/20) including environmental biomonitoring studies (4/20); only two publications addressed occupational exposure. Most of the studies were from Europe (7/20) and Asia (7/20); two studies (*Emeny et al 2019; McKelvey et al 2018*) were conducted in the USA, and the remaining studies (4/20) were from Latin America, Canada, and Australia.

Similar to the main review findings, mercury concentrations in biofluids and tissues represented a subclinical outcome most frequently evaluated in publications (12/20) from the addendum review. Among studies evaluating *non-occupational exposure*, increased mercury levels in relation to dental amalgam were reported in blood (*Bilak et al 2018; Snoj Tratnik et al 2019*), urine (*McKelvey et al 2018; Padmakumar et al 2019; Pirard et al 2018; Snoj Tratnik et al 2019*) and breast milk (*Vollsert et al 2019*), but not in hair (*Okati and Esmali-sari 2018*).

Per one of the US studies (*McKelvey et al 2018*) using the New York State and the National Health and Nutrition Examination Surveys (2003-2004 and 2013-2014), the proportion of blood mercury levels of ≥5

µg/L (*i.e.,* the reportable level in New York State) was shown to decline among adult New Yorkers within the 10-year study period. The highest 95th percentile urine mercury concentration was associated with ≥5 teeth with amalgam ("silver-colored") fillings (4.06 µg/L; 95% CL= 3.1, 5.9), and geometric mean urine mercury levels were associated with increasing number of fillings in the adjusted model (P< 0.001). Notably, the observed association between urine mercury (which virtually represents the inorganic form) and fish/seafood consumption (which represents the organic, predominantly methylated, mercury) was at least in part explained by demethylation of methylmercury in the intestine prior to elimination via urine.

In a Norwegian study on mercury concentrations in breast milk (*Vollset et al 2019*), mercury was detected in 100% of the study samples, with the median mercury concentration of 0.20 µg Hg/kg. With both number of amalgam fillings and high fish consumption identified as significant predictors, only 10% of variance in mercury concentrations in breast milk from Norwegian mothers was explained by the seafood intake alone, compared to 46% when considered together with amalgam fillings.
Among studies on *occupational exposure* (both of which were conducted outside of the US), a Sri Lankan study (*Wijesekara et al 2018*) reported higher hair mercury levels among dentists *vs*. controls, and a Canadian study (*Warwick et al 2018*) suggested that the mercury vapor levels created by a high-speed dental drill may exceed the safety thresholds.

Among publications on clinically manifested adverse outcomes in relation to dental amalgam, potential *neurotoxicity* was addressed in 5/20 publications. In the study using spectral domain optical coherence tomography (*Bilak et al 2018*), the volumes of ganglion cell and inner plexiform layers were reduced in the amalgam group *vs.* controls; the number of amalgam fillings positively correlated with mercury levels and Hg/BMI ratio, whereas the inner plexiform layer volume negatively correlated with blood mercury levels and Hg/BMI ratio. In a Taiwanese study employing a nationwide database to investigate the risk of ADHD in relation to dental amalgam (*Lin et al 2018*), young individuals with ≥6 amalgam restorations had a higher risk of ADHD (HR=1.20, 95% CI=1.04-1.38) compared to those with alternative restorations; however, the result was found to be confounded by age. On the contrary, in a large Norwegian study (>65,000 participants) on possible associations between ADHD and prenatal exposure to maternal amalgam fillings (*Lygre et al 2018*), no statistically significant associations were found between number of teeth with amalgam fillings, their placement/removals during pregnancy, and ADHD symptoms in children of 3 and 5 years of age. In a study using the International Restless Legs Syndrome

Study Group questionnaire (*Szklarek and Kostka et al 2019*), the group with the highest number of amalgam fillings (7–13) had the greatest occurrence (77.8%) of restless legs syndrome: the number of amalgam fillings was identified as a sex/age-independent predictor: OR=1.20; 95% CI: 1.02, 1.42; P=0.021). In an Australian online case-control study (*Parkin Kullmann and Pamphlett 2018*), no evidence was found linking the risk of developing amyotrophic lateral sclerosis to mercury exposure (either from seafood or dental amalgam).

Oral mucosa and cutaneous manifestations were assessed in 3/20 publications. In a small study (n=24) evaluating OLL and OLP in relation to dental amalgam (*Karatasli et al 2018*), mercury was identified among the materials most commonly eliciting a positive patch test reaction, and 59% of the patch-positive patients showed sensitization to at least one amalgam component; among the patients who had their amalgam fillings replaced, complete healing after 3 months was noted when OLLs were in close contact with amalgam restorations. In a study evaluating metallothionein expression in OLP *vs.* amalgam-associated OLL (*Mendes et al 2018*), metallothionein levels were found to be related to OLP severity, suggesting possible biomarker role for differential diagnosis between OLP and OLL. A small study on gingival discoloration (*Ristic et al 2018*) showed that lesions known as "amalgam tattoo" may also appear due to restorations other than dental amalgam.

Among studies on *perinatal and infant outcomes*, the risk of *perinatal death* (stillbirth ≥22 weeks plus neonatal death 0–7 days after birth) was assessed in a large observational cohort of 72,038 pregnant women, which was derived from the Norwegian Mother and Child Cohort Study (*Björkman et al 2018*). The absolute risk of perinatal death was found to be increased in women with ≥13 teeth with amalgam fillings compared to those with none (0.67% and 0.20%, respectively). An increase from 0 to 16 teeth filled with amalgam almost doubled the likelihood of perinatal death (ORadj=1.915, 95% CI: 1.12, 3.28). Although the risk was suggested to increase in an exposure dose-dependent manner, the increased likelihood was mostly limited to the highest tested level of exposure (*i.e.,* ≥13 teeth with amalgam), possibly reflecting residual confounding (*e.g.,* the likelihood in the highest exposure group was much higher for participants with lower *vs.* higher education).

In the study on potential associations between prenatal mercury exposure due to maternal amalgams and *the occurrence of infant allergy and respiratory symptoms* (*Emeny et al 2019*), higher toenail mercury concentrations among mothers who ate fish during pregnancy were associated with variable

risks of respiratory infections and other respiratory symptoms among their infants. Among infants of mothers who did not consume fish, an elevated risk of upper respiratory infections requiring a doctor visit was found in relation to maternal amalgams during pregnancy: RR=1.5 (95% CI: 1.1, 2.1). However, amalgam fillings did not correlate with maternal toenail mercury levels supporting the utility of toenail measurements as a proxy for methylmercury exposure.

No publications assessing potential *nephrotoxicity* in relation to dental amalgam have been identified in the period corresponding to the addendum review.

Similar to the main review, the addendum review identified demographics-related modifying effects. In the New York State based study (*McKelvey et al 2018*), urine mercury levels were elevated among non-Latino Caribbean-born blacks; Asian New Yorkers had higher blood mercury concentrations compared to other racial/ethnic groups, and the highest prevalence of reportable levels among foreign-born adults of East or Southeast Asian origin was interpreted in relation to the most frequent fish consumption. In the study assessing perinatal death (*Björkman et al 2018*), a slightly increased risk in relation to dental amalgam was reported for girls (ORadj=1.053, 95% CI: 1.007, 1.101) but not for boys. In the Slovenian environmental monitoring study (*Snoj Tratnik et al 2018*), mercury concentrations were shown to decrease with age, and men had higher blood and urine mercury levels, compared to women.

Similar to the main review, many currently identified studies had limitations. Some studies mentioned dental amalgam as a variable of interest but lacked rigorous statistical assessment regarding dental amalgam exposure (*Carranza-Lopez et al 2019; Jose and Ray 2018; Padmakumar et al 2019; Wijesekara et al 2018*) or failed to provide exposure/outcome-related details such as mercury levels in breast milk (*Snoj Tratnik et al 2019)*. In studies not primarily focused on dental amalgam exposure, the assessment of amalgam-related associations was affected by high fish consumption in coastal regions (*Okati and Esmali-sari 2018; Padmakumar et al 2019*), or mining-related environmental contamination (*Snoj Trotnik et al 2019; Carranza-Lopez et al 2019*). In one of the studies on occupational exposure (*Wijesekara et al 2018*), blood concentrations of mercury among dentists were assessed as relatively safe (<10 ng/mL, or 10 ppb) based the assumed hair to blood measurement ratio (as 250:1) and despite the reported increase in hair mercury measurements among dentists *vs.* controls.

As pointed out by *Snoj Trotnik et al (2019),* the published data on mercury levels in breast milk are still scarce. Concerns about susceptible populations were further raised in the study reporting possible association between high-level dental amalgam exposure and increased risk of perinatal death (*Björkman et al 2018*); the association implicating dental amalgam in perinatal mortality was, however, affected by residual confounding (e.g., due to different education levels).

Importantly, methodological limitations may have affected mercury measurements in many if not all studies. As discussed by *Snoj Tratnik et al (2019)* and *McKelvey et al (2018)*, seafood consumption can contribute to urinary mercury levels (up to 30%), consistent with the suggestion that due to demethylation processes in the human body, a certain proportion of urinary mercury can originate from dietary consumption of fish/seafood, as first shown by a stable isotope technique in the study by *Sherman et al (2013)* referenced in the main review.

Since the publication by *Mortazavi et al (2014),* which was referenced in the main review, some additional publications[z] suggest the possibility of microleakage and mercury release from dental amalgam due to non-ionizing radiation (*e.g.,* MRI and cell phones). However, these studies were limited to bench testing and none of them reported epidemiologic/clinical evidence supporting putative *ex vivo* and *in vitro* effects, which precluded their inclusion in the current addendum review.

In summary, the current update that evaluated studies from October 2018 – August 2019 did not identify any findings that would change the main review's conclusion on the absence of sufficient evidence to determine that dental amalgam causes adverse health risks in the general population. However, the addendum review confirmed relatively higher levels of mercury measurements among dentists. Moreover, the high mercury vapor levels created by a high-speed dental drill were identified as a previously underrecognized source of occupational exposure (*Warwick et al 2018*). With several new

[z] The following articles regarding non-ionizing radiation effects were identified in the initial searches for this addendum review, but excluded during the 1st pass review:

Hasan, S. A., et al. (2018). "Effect of radiation from mobile devices on mercury leaching in dental practice." Drug Invention Today 10(Special Issue 2): 3094-3096.

Mortazavi, S. M. J., et al. (2019). "Synergistic effect of radiofrequency electromagnetic fields of dental light cure devices and mobile phones accelerates the microleakage of amalgam restorations: An in vitro study." Journal of Biomedical Physics and Engineering 9(2): 227-232.

Yilmaz, S. and M. Zahit Adisen (2018). "Ex vivo mercury release from dental amalgam after 7.0-T and 1.5-T MRI." Radiology 288(3): 799-803.

studies focusing on potential neurotoxicity, spectral domain optical coherence tomography-based assessment of the volumes of ganglion cell and inner plexiform layers was suggested as a non-invasive approach (*Bilak et al 2018*) and restless legs syndrome was suggested as a novel outcome (*Szklarek and Kostka et al 2019*) for assessing potential neurotoxicity of mercury from dental amalgam. In the absence of a consensus on mercury values tolerable in child development, the currently available data on dental amalgam exposure among susceptible populations (*e.g.,* pregnant women and their developing fetuses and infants) were still found to be critically lacking (*Snoj Trotnik et al 2019).* Moreover, the currently available evidence on both occupational and non-occupational exposures was consistently found to be subject to the mercury measurement related limitations due to possible *in vivo* methylation/demethylation of mercury species (*McKelvey et al 2018; Snoj Trotnik et al 2019)*.

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Appendices

Appendix 1: 2010 FDA Systematic Assessment of Peer Reviewed Epidemiologic Literature
Appendix 2: 2012 and 2014 FDA Systematic Assessment of Peer Reviewed Epidemiologic Literature of Amalgam Risks in Sensitive Populations

Appendix 1: 2010 FDA Systematic Assessment of Peer Reviewed Epidemiologic Literature

Purpose

The purpose is to update prior reviews of the literature with a review of recent epidemiological research on elemental mercury exposure related to dental amalgam.

Introduction[1]

Dental amalgam is a dental restorative material used for direct filling of carious lesions or structural defects in teeth. It is a heterogeneous intermetallic compound, consisting of liquid, elemental mercury and a powdered alloy composed of primarily silver, tin, and copper. Approximately 50% of dental amalgam is elemental mercury by weight. Dental amalgam has been on the U.S. market in its present form since the late 1800s. Over 50 million amalgam restorations are placed annually in the U.S.[2] The two components of dental amalgam, mercury and amalgam alloy, were initially classified as separate devices in 1987. In the early 1990's, the Assistant Secretary of Health charged the Committee to Coordinate Environmental Health and Related Programs (CCEHRP) with evaluating the relevant scientific literature regarding the risks and benefits of dental amalgam.

In 1993, the United States Public Health Service (USPHS) published the CCEHRP report on dental amalgam, which concluded that "current scientific evidence does not show that exposure to mercury from amalgam restorations poses a serious health risk in humans, except for a small number of allergic reactions. [3] This report also recommended a strategic plan for USPHS agencies for future research, education, and regulation of dental amalgam including:

- A comprehensive review of the scientific literature including identifying important gaps in the current knowledge about the effects of dental amalgam and alternative materials on the body,
- Educating dental personnel and consumers what is and is not known about the safety of dental amalgam, and
- Reclassifying the components of dental amalgam into a single classification regulation.

Several advisory committee meetings have been held on dental amalgam, notably:

- 1993-94 -- Dental Products Panel:
  - discussed the risks and benefits of dental amalgam,
  - stated that there were no major risks associated with encapsulated amalgam, when used as directed, but recognized there was a small population of patients who may experience allergic reactions to the materials in the device, and
  - recommended FDA reclassify the components of dental amalgam into a single class II regulation
- 2006 -- A joint committee of CDRH Dental Products Panel and CDER Peripheral and Central Nervous System Drugs Advisory Committee:
  - discussed FDA's draft White Paper on the latest peer-reviewed literature on dental

amalgam and
- identified gaps in the scientific knowledge, especially with respect to exposure limits and lack of attention to risk factors for sensitive subpopulations

In 2009, FDA issued a final rule[4] reclassifying all components of dental amalgam into Class II (Special Controls) (21 CFR 872.3070) and issued a guidance document [5] as the special control.

PETITIONS

Since the issuance of the final rule in 2009, FDA has received four petitions requesting a reconsideration of the rule. The petitions were filed by the following individuals.

- James Love/Robert Reeves (July 25, 2009)
- James Turner (September 2, 2009)
- James Love/Robert Reeves (September 3, 2009)
- Richard Edlich (January 14, 2010)

The petitioners raise myriad concerns, both scientific and administrative. Among the scientific concerns raised by the petitioners are the following:

- The epidemiological studies are not conclusive in establishing the safety of mercury released from dental amalgam.
- Adverse effects are associated with exposure to mercury from dental amalgam, including Alzheimer's disease, Parkinson's disease, multiple sclerosis, amyotrophic lateral **s**clerosis, severe autism, kidney dysfunction, hearing loss, allergy to mercury, and other adverse effects including periodontal disease, inflammation, idiopathic dilated cardiomyopathy, and bone loss.
- The final rule is based on an inadequate risk assessment for elemental mercury, especially with regard to FDA's use of EPA's reference exposure concentration (RfC) for mercury vapor as a reference exposure level (REL).
- The quantity of mercury absorbed by amalgam bearers exceeds minimal risk levels for mercury vapor.
- The conclusions that sensitive subpopulations are not at risk from amalgam are unfounded.
- The final rule does not consider amalgam's contribution to the total mercury body burden and the bioaccumulation of mercury. It may take years to observe the adverse effects of the slow accumulation of mercury in various tissues.

Based on the concerns raised, the petitions request that FDA either ban amalgam or place restrictions on its use, especially for pregnant women, children under six, and sensitive individuals**.**

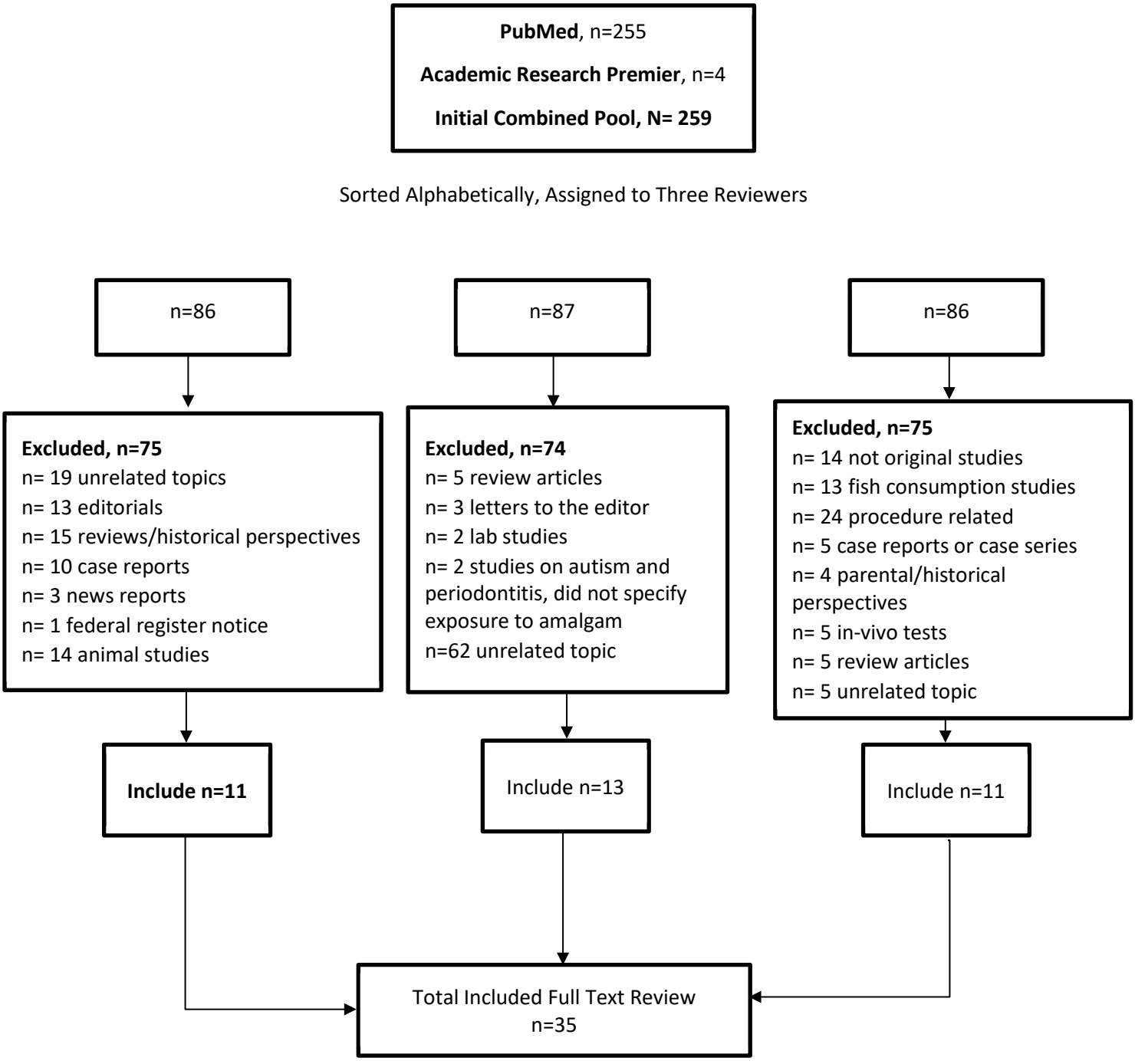
To respond to the petitioner concerns, FDA scheduled an Advisory Panel meeting on December 14-15, 2010. As part the preparation for this meeting, we conducted an update of the epidemiological literature from January 1, 2008 to November 11, 2010 at the request of the dental amalgam review team. The purpose was to update prior reviews on this topic.

Methodology

To identify papers for the review, the same search terms used in the 2006 FDA White Paper were used[6-7]: “mercury and (dental or dentist or dentistry or dentist)” OR “(amalgam or amalgam*) and (dental or dentist or dentistry or dentist* or filling or fillings)” OR "dental amalgam"
AND
“(adverse effects or adverse effect or adverse or to* or toxin* or toxic* or safety or fertility or infertility or reproduction or exposure or exposures)” OR "(adverse effects or risk or toxicity [Subheading] or mercury poising or poisoning [Subheading] or clinical trials or clinical trial [publication type] or equipment safety”

The process of article retrieval and selection is presented in Figure 1. The search resulted on 255 publications from PubMed. The search was replicated using Academic Search Premier and found four additional publications, making the initial pool of 259 publications. The publications were sorted in alphabetical order by first author and divided among three members of the team. Abstracts were read to find and retain only original human clinical studies in English that evaluated dental amalgam effects.

Figure 1 Retrieval of Publications



In the first 86 articles (which included those with no named author (e.g. institution or agency) a total of 56 articles were eliminated because they were not human clinical studies. The breakdown of these articles is as follows: letters/editorials (n=13), reviews/reports/historical perspectives (n=15), case reports (n=10), news (n=3), federal register (n=1), and other (n=14), which included studies in animals

(dogs and mice) and studies on extracted teeth. The full text was reviewed for the remaining 30 articles. Of these, eleven articles were in English and assessed effects of dental amalgam mercury in humans or assessed predictors and/or associations of dental amalgam mercury in humans. These articles were reviewed and included in this report.

In the second group, a total of 87 abstracts from the middle of the alphabet were reviewed. Of these, full text articles were obtained for 25 articles published in English that reported dental amalgam and mercury toxicity. The following articles were eliminated: 5 review articles, 3 letters to the editor, 2 lab studies, and 2 studies reporting the association of mercury with Autism and periodontitis that did not specify the specific exposure to dental amalgam. The remaining13 human studies reported the results of dental amalgam associated mercury exposure and were reviewed and included in this report.

Finally, the remainder included 86 abstracts at the end of the alphabet that were review. Seventy-five articles were eliminated from the review for the following reasons: papers were review articles/ reports/scientific or historical perspectives and not original studies (n = 14), studies focused on fish consumption and/or methyl mercury exposure (n= 13), studies were procedure/ performance related rather than amalgam effect (n= 24), articles were case reports or case series (n= 5), studies involved in vivo testing (n=5), and articles were parental or professional attitudes/perceptions (n= 4). The full text was reviewed for the remaining 22. Of these, 11 articles pertaining to studies of dental amalgam exposure in humans were retained and reviewed for inclusion in the report. Thus, 35 articles (Attachment A) were selected for in-depth analysis and are the subject of this review.

Studies evaluated the effect of dental amalgam exposure on clinical outcomes or mercury concentrations in blood, hair, urine and other body fluids. Studies were categorized by the focus of the study and whether the study evaluated clinical outcomes or laboratory measures of mercury. The 35 articles included in this literature review were categorized by the reviewers into the following subgroups by main focus: pregnancy, children, number of amalgams/removal of amalgams, occupational exposure, genetics, hypersensitivity/immunology/autoimmunity, and other.

Summary of Literature by Topic Area

Pregnancy

There were six studies which examined mercury exposure in relation to pregnancy and maternal/child health outcomes. All the pregnancy-related studies were observational. Each study had a specific focus, ranging from in-vitro fertilization outcomes to mercury levels in breast-milk and cord blood. The six studies are briefly described below, with additional information provided in Attachment A, Table 1.

One cross-sectional study from Saudi Arabia looked at the effects of mercury on the outcome of in-vitro fertilization treatment in 619 women.[8] Total mercury was measured in blood and follicular fluid, and no effects of blood or follicular mercury levels were found on pregnancy or fertilization outcomes after adjustment for various confounding variables. Predictors of mercury levels in blood included use of skin-lightening creams, while predictors of mercury levels in follicular fluid included number of dental amalgams. This study did not assess mercury levels in urine. Recommendations do not exist for safe or acceptable mercury levels in follicular fluid.

In a cross-sectional study from Slovakia, the relationship between maternal dental amalgam fillings and mercury exposure in the developing fetus was assessed using 99 mother-child pairs.[9] Maternal blood and cord blood specimens were collected to measure mercury concentrations. No cord blood mercury concentrations reached the level considered to be hazardous for neurodevelopmental effects in children exposed to mercury *in utero* (EPA reference dose for mercury of 5.8 µg/l in cord blood, based upon the NAS recommendation).[10] The number of maternal fillings was positively associated with the levels of mercury in maternal blood ($P<0.001$) and cord blood ($P<0.001$). No association was found between fish intake during pregnancy and maternal or cord blood mercury concentrations. This study did not evaluate health outcomes in children from fetal mercury exposure and this group of mothers had relatively low fish and seafood consumption compared to other populations.

A prospective study from Turkey evaluated maternal factors influencing breast-milk mercury levels, and the relationship between mercury levels and infant growth and development during the exclusive breastfeeding period and in the second year of life.[11] Forty-four healthy mother-infant pairs were enrolled. Breast-milk mercury levels showed no correlation with number of amalgam-filled teeth. Breast-milk mercury levels measured at 10-20 days postpartum showed no effect on infant weight,

length, head circumference or blood pressure in the two- year study period (P>0.05). Infant development was normal for all children at five months and two years postpartum regardless of milk mercury concentration. Breast-milk mercury was measured in a single sample and did not account for possible variations in mercury level with time of day, length of feeding session, and number of postpartum days. Also, the length of follow-up may be inadequate to observe any impacts of mercury on growth and development. Preterm and low birth weight infants were not included in the study, and therefore, results cannot be generalized to these potentially higher-risk populations who may have different susceptibility to mercury effects.

A case-control study in the U.S. examined the relationship between number of maternal dental amalgams during pregnancy and the risk of diagnosed autism (severe) in comparison to diagnosed autism spectrum disorders (mild) in children.[12] Qualifying participants (n=100) were recruited from patients presenting for outpatient genetic consultations. The children were previously diagnosed with autism; were at least 6 years old at the time of initial clinical presentation; and were born between 1990 and 1999. The mean number of maternal amalgams did not differ between those with a diagnosis of autism and those with an autism spectrum disorder (P=0.09). When maternal dental amalgams during pregnancy was treated as a binary outcome, children from mothers with 6 or more amalgams had 3.2 times greater odds of being diagnosed with autism (severe) vs. autism spectrum disorder (mild), compared to children from mothers with 5 or fewer amalgams (P=0.01). This model was adjusted for age, gender, race, and region of residency. However, important confounding factors, such as other sources of maternal and child mercury exposure like maternal and child fish consumption, both maternal and child environmental sources, and postnatal Thimerosal-containing vaccines, were not measured. Also, this study did not examine a biologic measure of mercury. It is possible that other maternal factors related to having a higher number of dental amalgams could contribute to risk of autism diagnosis in children.

In a cross-sectional study from two cities in Sweden, 100 pregnant females were sampled for total blood mercury and total hair mercury.[13] Using multiple linear regression, blood mercury was related to the number of fish meals per week and to the number of amalgam fillings. Females from the coastal city had significantly higher hair mercury levels compared to females from the inland city. All levels were below suggested biological reference limits. This study did not measure clinical outcomes for the mother or infant and did not assess urine mercury levels.

A Norwegian cohort study aimed to identify factors associated with amalgam fillings in pregnant women and to obtain information about dental treatment.[14] A total of 67, 355 pregnancies were included where information had been collected at the 17th and 30th weeks of pregnancy. Lower education, higher body mass index (BMI), older age, and smoking during pregnancy were associated with having more than 12 teeth filled with amalgam, compared with 0 to 12 teeth filled with amalgam. This study did not examine a biologic measure of mercury. In addition, this study did not measure clinical outcomes for the mothers or infants.

In summary, there were no associations found between blood or follicular mercury levels and adverse effects on in-vitro fertilization treatment outcomes of pregnancy and fertilization. Factors associated with higher number of dental amalgams during pregnancy included lower education, higher BMI, older age, and smoking. The number of maternal amalgam fillings was positively associated with mercury levels in maternal blood, follicular fluid and cord blood. The number of fish meals per week was also related to blood mercury levels during pregnancy. Breast-milk mercury levels showed no correlation with the number of amalgam fillings. In addition, breast-milk mercury levels showed no effect on infant weight, length, head circumference, blood pressure, or infant development. There was no difference in the number of maternal dental amalgams during pregnancy between children diagnosed with autism and children diagnosed with an autism spectrum disorder. When the number of maternal dental amalgams during pregnancy was dichotomized (≥6 vs. ≤5), children exposed to higher maternal amalgams had significantly greater odds of being diagnosed with autism, in comparison to an autism spectrum disorder. However, the clinical relevance of this cut point (≥6 vs. ≤5 maternal dental amalgams) is not apparent, and the categorization of this variable may be a marker for some other unmeasured factor. All these results are from single studies, and therefore more information is needed before any conclusions can be drawn. The major limitation for this group of studies is that mercury speciation was not done, which means the biologic measurements captured total mercury exposure from all different sources. Only one study examined the relationship between maternal mercury levels (breast-milk) and infant health outcomes, in which mercury levels showed no correlation with number of dental amalgams and therefore mercury was likely attributed to other sources or a combination or sources. More well-designed studies are needed to directly assess the effect of mercury from maternal dental amalgams during pregnancy on infant and child health outcomes.

Genetics

There were three studies which examined associations between polymorphisms and mercury exposure on human mood and neurobehavior. These genetic-related study reports were different analyses of the same occupationally-exposed study cohort group, which was comprised of dentists and dental assistants from the state of Washington. The three study reports are briefly described below, with additional information provided in Attachment A, Table 2.

Male dentists and female dental assistants practicing in the U.S. were recruited for a cross-sectional study to examine the interaction effect of urinary mercury concentration and the serotonin transporter gene-linked polymorphic region (5-HTTLPR) polymorphism on neurobehavioral and mood domains.[15] There was evidence of an additive effect for urinary mercury and 5-HTTLPR polymorphism in both groups for specific behavioral domains. This study contributes to the growing literature on genetic determinants of mood and behavior that potentially increase susceptibility to mercury toxicity in humans. However, there was no control group of persons without occupational exposure to mercury, and therefore this study does not represent the general population of adults and children with lower-level mercury exposure.

In another analysis from the same cohort of male dentists and female dental assistants in the U.S., the associations between 5-HTTLPR polymorphism, dental mercury exposure, and neurobehavioral self-reported symptoms were examined.[16] There were no consistent associations found between urinary mercury concentration and any category of symptoms. However, associations were observed between increased symptoms of depression, anxiety, and memory and the 5-HTTLPR polymorphism involving two copies of the short allele (full mutation), but not with the polymorphism involving only one copy (heterozygous). This pattern demonstrates a gene–dose relationship for symptom reporting. These findings are of interest in terms of further defining individual sensitivity to mercury neurotoxicity in humans. Again, there was no control group of persons without occupational exposure to mercury, and therefore this study does not represent the general population of adults and children with lower-level mercury exposure. Also, because no associations were observed between urine mercury levels and

symptoms, the gene-dose relationship for symptom reporting may be due to factors other than dental mercury exposure.

Lastly, data from the cohort of dentists and dental assistants was used to examine associations between a functional single nucleotide polymorphism (Val158Met) in the gene encoding the catecholamine catabolic enzyme catechol O-methyltransferase (COMT), dental mercury exposure, and self-reported symptoms and mood.[17] There were no consistent associations found between urinary mercury concentration and any category of symptoms. However, associations were observed between increased symptoms and the COMT polymorphism involving the double allelic substitution (full mutation) compared to subjects with no substitutions. Associations with mood were limited to polymorphism status among female dental assistants. These findings provide further evidence of genetic factors potentially affecting human susceptibility to the toxic effects of mercury. There was no control group of persons without occupational exposure to mercury, and there may be other factors in addition to gender and dental mercury exposure that affect the association between Val158Met COMT and mood.

In summary, there were no consistent associations found between urinary mercury concentration and any category of self-reported neurobehavioral symptoms and mood among this study cohort of male dentists and female dental assistants. There was evidence of an additive effect for urinary mercury and 5-HTTLPR polymorphism on specific behavioral domains. In addition, increased symptoms were associated with the 5-HTTLPR polymorphism full mutation and the COMT polymorphism full mutation in this occupationally-exposed group. Because all of the genetic-related results are from the same study cohort, it would be important to replicate these findings in other populations including both occupationally-exposed and non-occupationally exposed persons. These studies provide further evidence of genetic factors that potentially increase human susceptibility to mercury toxicity. More research is needed to continue to define individual sensitivity to mercury.

Hypersensitivity/Immunology/Autoimmunity

There were four studies which examined the relationship between mercury and immunologic outcomes. These studies are briefly described below, with additional information provided in Attachment A, Table 3.

A retrospective chart review in England evaluated the relationship between patient complaints of oral and medical symptoms related to perceived mercury toxicity from amalgam fillings and mercury levels in their blood and urine.[18] Presenting complaints included oral cavity symptoms (soreness, pain, metallic tasted, hypersalivation), neurological symptoms (memory loss, confusion, headaches and dizziness), musculoskeletal (joint ache, fatigue and malaise), and anxiety and depression. All patients reporting oral symptoms (n=27) were patch tested using the European Standard and Dental Material Series, and 26 were found to have a negative response while 1 patient had a weak response to mercury amalgam. Blood mercury levels were higher in patients with presenting complaints in the oral cavity. No other presenting complaint category was associated with blood or urine mercury. No presenting complaint categories were associated with the number of amalgams, and number of amalgams was not associated with blood or urine mercury. This study had a small sample size (n=56) and patients did not undergo psychological evaluation to determine any amount of somatization of symptoms from mercury toxicity. Also, because the number of amalgams was not associated with blood or urine mercury levels or with any of the presenting complaint categories, there may be other sources of mercury which contributed to the association between blood mercury levels and patients' oral cavity symptoms.

A sub-study of the New England Children's Amalgam Trial (NECAT) evaluated participants for in vitro manifestations of immunotoxic effects of dental amalgam.[19] Fifty-nine children were assessed for total white blood cell counts, specific lymphocyte (T-cell and B-cell) counts and lymphocyte, neutrophil and monocyte responsiveness across a five-year period. There were no statistically significant differences observed between treatment groups (amalgam vs. composite) in terms of the distribution of lymphocytes, monocytes and neutrophils. In the amalgam group, a slight but non-statistically significant decline in responsiveness of T cells was observed at 5 to 7 days after amalgam treatment; however, this did not persist at 6, 12 or 60 months of follow-up. Due to the small sample size of sub-study participants, there was limited statistical power and it is challenging to draw definitive conclusions. Also, the authors mention secondary analyses which looked at urinary mercury excretion and immune function; however, the data was not shown. Therefore, this study did not report a biologic measure of mercury.

A case-control study in Croatia examined the association between oral lichenoid reactions (OLR) and amalgam restorations, and examined the salivary concentrations of interleukin-6 (IL-6) and interleukin-8 (IL-8) before and after replacement of amalgam restorations. [20] Twenty patients with OLR were compared to 20 healthy volunteers. The patients with OLR were skin patched tested, and 80% (16/20)

showed a sensitization to inorganic mercury or amalgam. The patients with OLR then had their amalgam fillings completely replaced with composite resin, gold, porcelain or a combination of these materials, and 16 of 20 showed complete healing of OLR while 3 patients had marked improvement and only 1 patient showed no improvement. Saliva samples taken from the patients before and after amalgam replacement showed that levels of IL-6 and IL-8 were significantly higher before replacement than after replacement. In the healthy volunteers, levels of IL-6 and IL-8 did not differ significantly between measurements. While amalgam filling replacement lowered the pro-inflammatory cytokine values in OLR patients to levels corresponding to a healthy control group, the sample size was small, and it is unclear if any of the healthy volunteers also had dental amalgam fillings. Also, a biologic measure of mercury was not performed.

In Italy, a cross-sectional study was conducted to test the occurrence of specific antibodies to antiglomerular basement membrane (anti-GBM-IgG) among patients with suspected adverse effects to mercury from dental amalgam fillings.[21] Twenty-four patients who had been referred for symptoms possibly related to dental amalgams were included. From standard and dental patch tests, 33.3% (8/24) were diagnosed with an allergy to mercury. None of the patients showed evidence of anti-GBM autoimmunity. Data was also analyzed by subgroups of patients with strong allergy to mercury and patients with past thimerosal-containing vaccines, and again there was no evidence of anti-GBM autoimmunity. However, the total sample size was small, and serum levels of anti-GBM-IgG are only one marker of kidney function. Also, this study did not include a biologic measure of mercury.

In summary, among patients presenting with symptoms possibly related to mercury from amalgam fillings, 3.7% to 33.3% had allergic responses to mercury. Among patients diagnosed with oral lichenoid reactions (OLR), 80% had allergic responses to mercury. There was no evidence of immunotoxic effects of dental amalgam mercury in a group of children and a separate group of adults as measured by white blood cell counts and specific serum antibodies to antiglomerular basement membrane, respectively. However, these studies had small sample sizes (range of 24 to 59 participants) and were not necessarily powered to detect a difference in outcomes or representative of a generalized population. There was evidence from one study to suggest that patients with OLR should have their amalgam fillings completely replaced with other materials for healing of OLR to occur and to lower the pro-inflammatory cytokine values in the saliva. More studies are needed that directly assess the effects of mercury from dental amalgams on patient symptoms and immunologic outcomes.

Exposure in Children

Eight (8) articles relevant to dental amalgam treatment in children ages 6-12 years at studies' inception were reviewed. These articles include the following types of studies: 3 randomized controlled trials, 2 secondary analysis of RCTs, 1 exploratory study, 1 comparative study and 1 cohort study. Four of the eight articles evaluated mercury effect on renal function (nephrotoxicity), 4 assessed neurobehavioral and/or neuropsychological performance, and 1 compared porphyrin excretion between neurotypical and autistic children (one article is discussed under both sections of renal function/nephrotoxicity and neurobehavioral/neuropsychological performance). These studies are briefly described below, with additional information provided in Attachment A, Table 4.

Two study reports from the Casa Pia children's Amalgam trial[22-23] in Portugal, evaluated mercury effects on the renal function of 479 to 507 children aged 8-18 years. The studies computed creatinine adjusted values and adjusted for group differences at baseline. No significant differences in the urine excretion of porphyrins of interest or biomarkers of renal integrity (glutathione S-transferase-alpha and -pi, and albumin) between treatment groups (amalgam versus composite) were found. However incipient increases in urine concentration of treatment-specific porphyrins: penta-, precopro-,and coproporphyrins were observed in younger subjects with dental amalgams compared to those with composite resins (8-9 years at baseline) in the Woods et al 2009 study.[23] The observed differences between amalgam and no amalgam groups were not statistically significant, possibly due to the small number of subjects in each group, additionally, this study had a low follow up rate at 7 years.

Researchers conducted a secondary analysis of the NECAT data[24] on children 6-10 years who were randomized to one of two treatment groups- Amalgam (n=267) or composite (n=267) to evaluate the effect of urine mercury from amalgam exposure on subjects' kidney function. They measured urine levels of renal injury biomarkers: albumin, alpha-1-microglobulin (A1M), gamma-glutamyl transpeptidase (gamma-GT), and N-acetyl-β-D-glucosaminidase (NAG). Three predictors were used for

each outcome: treatment group; number of amalgam and composite, and urine mercury levels. Models used for analysis (ANCOVA and logistic regression) controlled for randomization stratum, baseline covariates, urine creatinine concentrations storage time etc. They found no significant differences between treatment groups in average levels of renal biomarkers. The overall differences between groups for high level values of renal biomarkers were not statistically significant for A1M, gamma-GT, or NAG. However a significant increase in the prevalence of microalbuminuria (MA, urinary albumin > 30 mg/g creatinine) was found among children in the amalgam group in years 3–5 (adjusted OR 1.8; 95% confidence interval, 1.1–2.9) compared to children in the composite group (10 children in the amalgam group had MA in both years 3 and 5, versus 2 children in the composite group ($p = 0.04$, Fisher's Exact test). There was no significant increase in microalbuminuria with increasing number of amalgam fillings ($p= 0.30$) or urine mercury excretion ($p=0.71$). It is unclear whether the microalbuminuria that occurred among children in the amalgam group in years 3-5 will be persistent or is reversible. This study may have lacked power to detect effect that occurs only in a small susceptible fraction of children. The long storage times of urine may not have been optimal for accurate detection of biomarkers. A follow up period of more than 5 years (since this study was 5 years in length) may be needed to detect effects of exposure to mercury from dental amalgam.

An observational study[25], of children aged 7-11 (Amalgam group n = 198, Reference/No Amalgam group n = 205) from China, found no associations between any exposure indicator (urine mercury level, time since first amalgam treatment, total number of amalgam fillings, total number of visible amalgam surfaces, cumulative exposure index) and two biomarkers of renal function, albumin and *N*-acetyl-ß-D-glucosaminidase (NAG) in urine after controlling for potential confounders age, sex, family income and fish consumption. This study had small number of amalgam fillings (mean=2, range 1-7) among children in the amalgam cohort and this may have contributed to the study's inability to find association between the exposure indicators and biomarkers of renal function. The short mercury exposure time of 31 months may be insufficient time to detect an effect.

With regards to neurobehavioral or neurological performance, as part of the of the New England Children's Amalgam Trial (NECAT), the authors of a study evaluated amalgam effects on psychosocial function of children aged 6-10 years (Amalgam group n= 197, Non Amalgam group n = 198) in relation to three indices of amalgam exposure: treatment assignment, surface years of amalgam, and urinary mercury excretion.[26] The primary psychosocial outcome was score on the parent-completed Child

Behavior Checklist (CBCL) done at baseline and 5 years. Treatment groups were compared in terms of the change in CBCL scores over time, adjusted for randomization stratum, baseline score and baseline covariates (age, sex, socio-economic status family stress etc). Significant differences were found in areas of Internalizing, Total problem behaviors, the competence subscale of Activities, and two behavior subscales of Anxious/Depressed and Delinquent behaviors that tended to favor the amalgam group. Scores of amalgam group decreased more than Non–Amalgam group. Only Total Problem Behavior (global CBCL) was found significantly associated with surface years of amalgam. Children in the amalgam group showed greater improvement in behavior scores over time. Mean urinary mercury excretion between years 3 and 5 of follow-up was not significantly associated with any CBCL global score. No evidence that indicated an association between mercury exposure from dental amalgam and adverse psychosocial outcomes was found over the five year period.[26] The authors of this study indicated that amalgam exposure dose in study subjects could have been less (number not stated) than noted in other studies such as the Casa Pia Trial.[22-23] Secondly, the authors note that the ages of the subjects (6-10 years at baseline) may not be the period of greatest susceptibility to elemental mercury. Therefore, the results of this trial cannot be generalized to children younger than 6 yrs, especially to the fetus, known to be particularly sensitive to other forms of mercury. It is unclear why the results of certain scores (Internalizing, total problem scores, the competence subscale of activities, and two behavior subscales of Anxious/Depressed and Delinquent behaviors) were better in the amalgam group than that of children in the non-amalgam group.

In a large longitudinal randomized trial[27]researchers evaluated neurological outcomes in children with and without mercury exposure from dental amalgam over 7-year period and found no significant differences between treatment groups in any of the neurological measures (neurological hard signs, presence of tremor and neurological soft signs). Exposure to mercury from all sources besides dental amalgam was equivalent between the two treatment groups, the contribution of dietary mercury was similar between groups and there was no difference in vaccination history. Results are consistent with other previous large trials.

The authors evaluated findings of children enrolled in the NECAT[28] and measured their hair mercury concentration prior to randomization to Amalgam or composite treatment group. The study observed no significant adverse neuropsychological effects among children with hair mercury below 1.0µg/g but there are indications that neuropsychological test scores of children with hair Hg greater than 1.0µg/g

were lower than those with hair Hg less than 1.0µg/g. However, the number of children with hair mercury greater than 1.0µg/g was limited. Therefore, an inference of dose dependent relationship cannot be satisfactorily drawn.

Researchers conducted an observational study[26] to evaluate neurobehavioral and neuropsychological performance of children aged 7-11 (Amalgam group n = 198, Reference/No Amalgam group n = 205), with and without dental amalgam treatment. Exposure indicators measured include urine mercury and total number of amalgam fillings. Controlling for age, sex, family income, fish consumption, parent education and grade level, they found no statistically significant difference between Amalgam group and Non- Amalgam group in neurobehavioral and neuropsychological test scores (assessed by Child Behavioral Check List and Eysenck personality questionnaire) or intelligence test scores. School performance was not associated with urinary mercury levels or number of amalgam fillings. This study had a small sample size and subjects had a small number of amalgam fillings (mean= 2, range 1-7). In addition, the short mercury exposure time of 31 months may be insufficient time to detect effect. As a cross-sectional study it is uncertain if mercury exposure preceded outcome.

There was a study that evaluated porphyrin excretion between neurotypical and autistic children. An exploratory study[29] evaluated porphyrin excretion in neurotypical (NT, n= 59) and autistic (AU, n= 59) children and found that among males 2- to 12-year old, the mean concentrations of hexacarboxyl ($p < 0.01$), pentacarboxyl ($p<0.001$)-, and copro- ($p<0.009$) porphyrins were significantly higher among AU compared with NT groups (ANOVA *F*-test). In contrast, mean Uro- and precoproporphyrins concentrations are comparable between NT and AU children of the same age ranges. Mercury exposure appears not to have contributed to the differences in porphyrins measured between the two groups given that no differences were found between NT and AU in urinary Hg levels or in past Hg exposure determined by fish consumption, number of dental amalgam fillings, maternal exposure to mercury during pregnancy or vaccines received in total prior to 2002 when thimerosal an organomercurial compound was eliminated from vaccines. This finding of suggested disordered porphyrin excretion among some AU subjects needs confirmation in larger studies.

In summary, the studies reviewed thus far, both randomized trials and observational do not provide evidence of detrimental effect of amalgam-related mercury exposure toxicity on kidneys,

neurodevelopmental or psychosocial function of children aged 6-18 years studied. However, incipient increases in urine concentrations of porphyrins observed in one of the studies may be indicative of mercury exposure. In one study, microalbuminuria was associated with amalgam at ages 3-5 years. The implications of these findings are unclear from the studies reviewed.

Additionally, among males 2- to 12-year old, the mean concentrations of hexacarboxyl, pentacarboxyl-, and copro-porphyrins were significantly higher among AU compared with NT groups. In contrast, mean Uro- and precoproporphyrins concentrations are comparable between NT and AU children of the same age ranges. However, there were significant limitations to this study including a small sample size, no validation of other sources of mercury exposure, environmental and occupational exposure sources were not assessed and there was no unaffected comparison group.

Number of Amalgam Exposure/Removed

There were seven articles regarding exposure to mercury from the number of amalgams or amalgam removal. They include the following study types: 1 randomized control, 1 exploratory, 1 longitudinal and 3 cross-section studies. These studies are briefly described below, with additional information provided in Attachment A, Table 5.

The authors conducted a randomized study[30] that investigated the effect of dental amalgam removal and co-exposure from dietary organic mercury and found rapid drop in plasma and red cell inorganic mercury after amalgam removal, stabilizing after 60 days while concentrations of organic mercury in plasma remained unchanged. An increase in erythrocyte organic mercury occurred following removal of cellular inorganic mercury. This was attributed to binding of organic mercury to cellular site previously occupied by inorganic Hg. Urine concentration and excretion of total mercury were similar to plasma inorganic Hg levels. The daily dose of mercury absorbed from high amalgam exposure was estimated to be below the tolerable dose of 30 µg (WHO, 1990).[31]This study had a small sample size.

In an exploratory study of using RCT data,[32] the authors evaluated the effect of removal of amalgam fillings on patients' subjective symptoms and psychometric variables. Results showed that patients symptoms decreased after amalgam removal but there was no statistically significant difference between treatment groups in the decrease of symptoms after intervention (amalgam removal versus

health promotion with no amalgam removal). No correlation was found between mercury levels and psychological distress or health related quality of life. A significant decrease in urine mercury levels, however, was observed after amalgam removal. This study had a small sample size and may lack power to detect a difference. Additionally, patients were not blinded to treatment groups, the study period was short and may not have been sufficient to observe changes in symptoms.

The authors used data from the NECAT[33] and evaluated predictors of urine mercury in study children after dental amalgam exposure. Current number of amalgam surfaces was identified as the most predictive amalgam measure for current U-Hg excretion, whereas posterior occlusal surface-years of amalgam was most predictive for cumulative U-Hg. This study had no comparator.

Two cross-sectional studies found in three study reports evaluated the number of amalgam fillings and mercury levels in body tissues or fluid. First researchers found that among kidney donors, kidney mercury levels, measured from the cortex, increased with total number of amalgam fillings and kidney mercury increased by 6% with every additional amalgam surface.[34] Given that only small biopsy samples could be obtained from living donors, mercury concentrations from samples could be imprecise measure for whole kidney mercury if concentrations are not uniformly distributed in the kidney. Although study did not speciate mercury, fish consumption had no impact on the findings, and the authors concluded that the bulk mercury could be assumed to be inorganic mercury from dental amalgams.

In a second observational study, the authors measured mercury level in hair and saliva and evaluated the relationship between mercury concentrations in saliva and hair with the number of amalgams.[35] Mercury concentrations in saliva samples were significantly higher than in hair samples, and number of amalgams was highly correlated with both hair and saliva mercury concentrations. The study omitted occupational exposure and fish consumption (low in the study population) but did not measure other potential sources of mercury exposure such as cosmetic materials or hair shampoos.

Researchers conducted a cross-sectional study involving 39 female healthy subjects with 6 or more amalgam fillings and investigated the possibility that amalgam fillings might have a detrimental effect on auditory functions (hearing). [36] The result indicated that for the female participants having more

amalgam was associated with a deterioration of high frequency hearing acuity, 8 kHz and above, suggesting a dose- dependent effect of amalgam on hearing. No significant correlation between the number or score of composite fillings and auditory threshold was observed in the composite group. The observed effect was found not related to noise damage from the drilling process. This study had a small sample size and it is unclear how many patients were in each group (Amalgam versus Composite). In addition, participants had a mixture of filling types and their categorization is unclear. Nonetheless, measurement of hearing thresholds in patients was blinded, strengthening the validity of the study.

Melchart D, et al[37] investigated whether the measurements of mercury (Hg) concentration is appropriate for identifying patients with health complaints attributed to dental amalgam. Hg in erythrocytes, plasma, urine, and saliva was determined in 27 patients with complaints of health problems attributed to amalgam, 27 healthy volunteers with at least 5 amalgam fillings, and 27 healthy amalgam-free volunteers. The results showed that concentrations of inorganic mercury in blood and total mercury in urine and saliva differed significantly between subjects with amalgam fillings and amalgam-free volunteers, but not between symptomatic patients and healthy volunteers with amalgam fillings. Urine Hg levels tended to be better correlated with blood than with saliva data. Levels of organic Hg were similar among all groups. Therefore, concentrations of total and inorganic mercury in body fluids could not distinguish between symptomatic and healthy amalgam bearers. The limitation of the study is that symptomatic patients and the two control groups were not comparable on several factors. The symptomatic patients were older, less educated, more likely to be married than the rest of 2 groups. Also, they had longer period of exposure to amalgam than health amalgam bearers, and more likely to be male than the healthy volunteers.

In summary, the number of dental amalgams appears to correlate strongly with mercury content in kidney, urine, saliva and hair. Conversely amalgam removal was found to be associated with drop in plasma and urine inorganic mercury. In contrast, dental amalgam removal was not associated with decrease in patients' subjective symptoms or psychological stress; however, follow-up post-removal was limited. A dose-dependent effect was observed between mercury exposure from dental amalgam and poor auditory threshold at high frequencies. An increase in the number of amalgams was associated with a deterioration of higher frequency auditory thresholds in the 40-45 age group of females studied. Confirmation of these findings in a larger study is needed. Studies such as Weidenhammer et al, 2010 [32]

add to the inconsistencies that exist in literature regarding low level mercury exposure and reported symptoms. Larger and longer-term studies are necessary to evaluate these findings.

Occupational Exposure to Mercury and Potential Health Impact

There were four studies which examined the relationship between occupational exposure to mercury and clinical outcomes. These studies are briefly described below, with additional information provided in Attachment A, Table 6.

Moen, BE, et al [38] conducted a cross-sectional study to compare the occurrence of neurological symptoms among dental assistants likely to be exposed to mercury from work with dental filling material, compared to other health personnel (assistant nurse) with no such exposure. The study invited 41 registered dental assistants in Hordaland county of Norway and 64 randomly selected registered assistant nurses. All subjects completed a self-administered, mailed questionnaire, with questions about demographic variables, life-style factors, musculoskeletal, neurological and psychosomatic symptoms (Euroquest). The results showed that both groups had similar educational levels. The dental assistants were older, had more years at work, and higher alcohol consumption than the assistant nurses, while more assistant nurses were smoking. In addition, the dental assistants reported a significantly higher occurrence of neurological symptoms (primarily with hands and arms); psychosomatic symptoms, memory loss, concentration difficulties, fatigue and sleep disturbance, but not for mood, after adjusting for age, education, alcohol consumption, smoking and personality traits. The authors concluded that the higher occurrence of neurological symptoms among the dental assistants may be related to their previous work exposure to mercury amalgam fillings, but further clinical study is needed to assess the clinical importance of the reported symptoms. The limitations of the study were lack of specific information about the individual exposure to mercury and other neurotoxins during the work, as well as healthy worker effect due to the cross-sectional design of the study.

De Oliveira et al[39] evaluated the systemic mercury levels in urine of patients and dental school students caused by exposure to silver amalgam. The study included 40 urine samples from 20 subjects, which were divided into four sampling groups with 10 subjects in each group: Group 1 (G1) included dental school students before their first occupational contact (G1A) and the same students after their first contact (G1B); Group 2 (G2) composed of patients who needed replacement of amalgam restorations

before amalgam removal (G2A) and the same patients after amalgam removal (G2B). The age of subjects in G1 was 19 to 21 years (seven men and three women) and the age of subjects in G2 was 20 to 35 years (six women and four men). The results showed urinary mercury levels measured at 48-72 hours after the exposure increased in all subjects, with some of whom showed an increase >100% that was a statistically significant difference between dependent groups G1A and G1B (p=0.004) as well as between G2A and G2B (p=0.005). However, urine mercury levels in all the participants were below the limits of biologic tolerance as recommended by WHO.[40] The authors concluded that occupational exposure to dental amalgam poses a potential risk of increasing systemic mercury levels. The limitations of the study included the small sample size for each group and lack of details on other potential source of mercury exposure.

Farahat SA, et al[41] investigated mercury body burden in dental staff in Egypt, the relation of this burden to the potential impact of mercury on thymus gland hormone level (thymulin) and explored the mercury effect on nitric oxide synthetase as a possible mechanism of immunotoxicity. The study was a matched case-control study design. The population consisted of 39 working dental staff (n = 39) (21 dentists and 18 nurses) and 42 medical/nursing staff as control matched by age, gender, social economic status, number of dental fillings and fish consumption. Each subject had detailed personal (including fish consumption), occupational and medical histories taken, as well as urinary mercury (U-Hg) and blood mercury (B-Hg) measured as indicators of mercury body burden. The study results showed significantly higher U-Hg (19.76 ± 1.37 µg Hg/g creatinine) and B-Hg (7.82 ± 0.97 µg/L) levels in the dental staff compared to the controls (5.44 ± 1.18 µg Hg/g creatinine and 4.82 ± 0.75 µg/L respectively, P<0.001). Also, the elevation of mercury body burden was associated with significant reduction in thymulin hormone blood level and nitric oxide parameters. These results were more evident in the dental nurses. In addition, there was also a significant positive correlation between the duration of work and both U-Hg and B-Hg levels among dental staff ($r = 0.60$, $P < 0.05$). The authors commented that the data suggested dentists and dental nurses have significant exposure to mercury which may have negative impact on thymus gland functions and the nitric oxide pathway is a possible mechanism for this impact. The major limitation of the study was small sample size.

Jarosinska D[42] conducted a cross-sectional study in Sweden, Italy and Poland to assess environmental and occupational exposure to mercury from mercury cell chloralkali (MCCA) plants and the potential association with biomarkers of early renal dysfunction. Questionnaire data related to the location of the

subjects' residence relative to MCCA plants and workplace, occupational history including possible exposure to mercury, number of teeth filled with amalgam, consumption of various types of fish, smoking history, and relevant medical history (kidney disease, diabetes, or hypertension) and urine samples were collected from 757 subjects. Of them, 179 were MCCA workers with occupational exposure to mercury and 578 were general population who either lived close to MCCA plants or in reference areas that were distant from MCCA plants. Urine samples were analyzed for mercury corrected for creatinine (U-HgC), alpha-1-microglobulin (A1M), N-acetyl-b-glucosaminidase (NAG) and albumin. Levels of kidney markers were compared in three U-HgC categories (<5.4, 5.41–17.3, and >17.3 µg/gC), and differences were tested adjusting for age and other covariates. In the general population, the median U-HgC was higher in Italian (1.2µg/gC) than in Polish (0.22µg/gC) or Swedish (0.21µg/gC) subjects, and there was no significant difference in urinary mercury in subjects living near MCCA plant as compared with those living in reference area. Dental amalgam, chewing on amalgam, and fish consumption were positively associated with U-HgC level. Regardless of amalgam fillings, urinary mercury was higher in women. No association between urinary mercury and kidney markers was identified in general population. While in MCCA workers and men, U-HgC was positively associated with the kidney markers, especially with NAG and to a lesser extent for A1M and albumin. The limitation of the study was that it did not focus on vulnerable groups, such as elderly, people with chronic diseases, pregnant women, or children; and not all subjects had been living in the respective areas for a long time.

In summary, Occupational exposure to mercury, likely from dental amalgam, was associated with a higher level of urinary and blood mercury levels among dental professionals. The potential negative impacts explored included the reduction of thymus gland functions and self-reported outcomes including a higher prevalence of neurological symptoms, psychosomatic symptoms, memory loss, concentration difficulties, fatigue and sleep disturbance among dental assistants compared to other medical professionals. However, it should be noted the limitations of these studies, i.e. cross-sectional in nature, small sample size, lack of information on individual exposure to mercury and other neurotoxins during the work, as well as a lack of an objective clinical assessment.

Other Studies related to Dental Amalgam and Mercury Effects

Three additional studies reported evaluation of dental amalgam and health outcomes or interactions with other health care activities. These studies are briefly described below, with additional information provided in Attachment A, Table 7.

Mortazavi SM et al[43] conducted a study to investigate how the exposure to radiation will affect the saliva mercury level among patients with dental amalgam fillings. In the first part of the study, 5 mL saliva was collected from 30 patients before and after MRI, with the magnetic flux density at 0.23 T and the duration of exposure to magnetic field at 30 minutes. The results showed saliva Hg concentrations of the patients before and after MRI were 8.6±3.0 and 11.3±5.3 µg/L, respectively ($p<0.01$). In the second part of the study, 14 female university students who neither used mobile phone nor had any amalgam restorations before were given amalgam restoration and then randomized into mobile phone user group and control group. Urine samples were collected before and after amalgam restoration. The results showed that urinary Hg concentrations of the students who used mobile phones were 2.43±0.25, 2.71±0.27, 3.79±0.25, 4.8±0.27 and 4.5±0.32 µg/L before and at days 1,2, 3 and 4 after the amalgam restoration respectively, whereas the respective Hg concentrations in the control group who did not use mobile phone were 2.07±0.22, 2.34±0.30, 2.51±0.25, 2.66±0.24 and 2.76±0.32 µg/L. There was a statistically significant ($p<0.05$) difference between the 2 groups. It was suggested that MRI and microwave radiation emitted from mobile phones significantly release mercury from dental amalgam restoration for several days after placement. The major limitation of the study was small sample size and lack of information on other potential source of mercury exposure such as fish consumption and environmental exposure.

Díez S, et al[44] conducted a cross-sectional study to investigate the hair mercury levels in 237 adults (115 females, 122 males) aged between 35–45 years old with absence of known occupational and/or environmental exposure to mercury. Information on age, gender, body weight, height, body mass index (BMI), fish consumption, number, surface and area of dental amalgam fillings was collected. Study participants were divided into three groups in accordance with fish consumption and dental amalgam: ANF (amalgam and no fish); NAF (no amalgam but with fish) and AAF (amalgam and fish). The mean of total mercury (THg) concentrations in hair for all 3 groups was 0.638 µg/g. The hair mercury concentration was significantly higher in AAF group (0.82 µg/g) compared to NAF (0.69 µg/g) and ANF group (0.46 µg/g). Men had higher mean hair mercury concentrations than women (0.71 versus 0.56 µg/g, $p=0.003$). There was no difference in hair mercury levels between those with amalgam fillings (0.62 µg Hg/g) and those without (0.69 µg Hg/g, $p=0.27$). However, significant differences in hair mercury were found between the groups that eat fish or do not eat fish (0.76 versus 0.46 µg/g, $p<0.05$). In multiple linear regression analysis, gender, age, number of amalgam fillings and fish consumption were significantly associated with increased total mercury in hair, but the fish consumption had the

largest partial correlation. The limitation of the study is that it did not speciate mercury and the age range of participants is limited therefore results are not generalizable to the overall adult population.

Dunn JE et al[45] analyzed the data from the New England Children's Amalgam Trial on the levels and correlates/predictors of scalp hair (H-Hg) and urinary (U-Hg) mercury over a 5-year period in 534 children. Repeated measures models were fit to determine significant correlates/predictors of hair and urine mercury. The average age was 7.9 years (range: 6–10 years). Mean H-Hg levels were between 0.3 and 0.4 mg/g over 5 years. 17–29% of children had H-Hg levels ≥0.5 mg/g, and 5.0 to 8.5% of children had levels ≥ 1 mg/g. The frequency of fish consumption was the most robust predictor of high H-Hg. Other significant predictors of H-Hg include the Boston (vs. Maine) site and being of ''other'' race (other than black, white, or Hispanic). U-Hg mean levels were between 0.7 and 0.9 mg/g creatinine over two years. 4% to 6% of children had U-Hg ≥ 2.3 mg/g creatinine. The number of amalgam restorations had a significant dose-response relationship with U-Hg level. Daily gum chewing in the presence of amalgam was also associated with high U-Hg. The limitations of the study were that it did not speciate mercury, and the stringent eligibility criteria for this clinical trial resulted in a study population with lower socioeconomic status than the general population, therefore is not a representative sample of the children in US. In addition, because this population had generally low levels of Hg, roughly half of the samples were below the level of detection. Imputation of these samples limits also the accuracy of the average Hg levels.

In summary, one small study suggested that low dose radiation from MRI and mobile phone use may increase the release of mercury from dental amalgam fillings, which certainly warrants a larger clinical study or bench top lab study to confirm the results. Two studies of hair mercury indicated that higher hair mercury levels were associated with age, gender (male), number of dental amalgams, but most strongly the fish consumption, whereas the number of amalgam restorations and daily gum chewing had significant relationship with higher Urinary mercury level.

Conclusions and Recommendations

Recent literature has evaluated several potential associations between dental amalgam exposure, elemental mercury and health outcomes. Most of these studies did not identify an association. There were, however, several findings of interest including:

- A positive correlation between the number of maternal amalgam fillings and increased mercury in maternal blood, follicular fluid, and cord blood.
- When the number of maternal dental amalgams was dichotomized to ≥6 vs. ≤5, there was a significant relationship between a child being diagnosed with autism versus autism spectrum disorders (ASD); however, autism is a multi-factorial syndrome and there is insufficient evidence of causality.
- The presence of microalbuminuria in children ages 3-5 exposed to dental amalgams and increases in the urine concentrations of porphyrins, both biomarkers of kidney injury.
- Among males 2 to 12 years old, the mean urine concentrations of hexacarboxyl, pentacarboxyl-, and copro-porphyrins were significantly higher among autistic children compared to those diagnosed with ASD.
- An additive effect of urinary mercury and 5-HTTLPR polymorphism on specific behavioral domains among dentists and dental assistants, and increased symptoms reported when this was a full mutation.
- Among patients presenting with symptoms possibly related to mercury from amalgam fillings, 3.7% to 33.3% had allergic responses to mercury.
- Among patients diagnosed with oral lichenoid reactions (OLR), 80% had allergic responses to mercury and most of these reactions resolved when amalgam fillings were removed.
- The number of dental amalgams and number of amalgam surfaces appear to correlate strongly with mercury content in kidney, urine, saliva and hair, a finding consistent with previous PHS and FDA reviews.
- A dose-dependent effect was observed between mercury exposure from dental amalgam and poor auditory threshold at high frequencies in a 40-45 age group of females studied.
- Occupational exposure to mercury was associated with higher urinary and blood mercury levels among dental professionals with an associated decrease in thymus gland function and increase in the self-reported prevalence of neurological symptoms, psychosomatic symptoms, memory loss, concentration difficulties, fatigue and sleep disturbance.
- Low dose radiation from MRI and mobile phone use may increase the release of mercury from dental amalgam fillings for several days after placement.
- The number of amalgam restorations and daily gum chewing had significant relationship with higher urinary mercury level in children.

These findings are limited by several concerns. Most importantly, mercury speciation was not done in any of the studies as biologic measurements were captured as total mercury exposure from all sources. Many are single studies with small sample sizes where comparisons were made on the same cohort, or only studied subjects who had an adverse health effect such as autism or hypersensitivity.

Additionally, most studies were not sufficiently powered to evaluate rare occurrences, nor was there a rationale for the length of follow-up to evaluate the effects of amalgam removal when adverse symptoms were identified. An example of a limited length of follow-up can be found following amalgam removal in patients with subjective symptoms where removal was found to be associated with drop in plasma and urine inorganic mercury but not associated with a decrease in patients' subjective symptoms

or psychological stress.[32] Another example is that the prospective randomized trials followed subjects for up to 7 years. It is possible that a longer length of follow-up may have demonstrated a different set of findings.

The genetic studies provide further evidence of genetic factors that potentially increase human susceptibility to mercury toxicity; however, all the genetic-related results were from the same study cohort. Therefore, it would be important to replicate these findings in other populations including both occupationally-exposed and non-occupationally exposed persons.

These findings suggest potential associations; however, none provide conclusive evidence related to exposure to dental amalgams with adverse health outcomes. In the case of pregnancy and children under age six, very little evidence exists regarding thresholds for concern or potential adverse outcomes. More well-designed studies are needed to directly assess the effect of mercury from maternal dental amalgams during pregnancy on infant and child health outcomes as well as individual sensitivity to mercury, immunologic and genetic outcomes and occupational exposure.

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Attachment A

Table 1 Pregnancy
Table 2 Genetics
Table 3 Hypersensitivity/Immunology/Autoimmunity
Table 4 Children
Table 5 Number of Amalgams/removals
Table 6 Occupational Exposure
Table 7 Other

1 Table 1 Pregnancy

Authors Country	Study Design Number of Subjects	Type of mercury studied Type of measure	Mercury effects studied	Cofactors Evaluated	Comparison group Single vs. Multi-site	Mean age (years)	Primary endpoint findings	Secondary endpoint findings	Mean follow-up and follow-up rate	Limitations
Al-Saleh et al.[8] Saudi Arabia	Cross-sectional; 619 women undergoing in-vitro fertilization (IVF) treatment	Total mercury; Whole blood and follicular fluid	The effects of mercury from different sources on IVF treatment outcomes of pregnancy and fertilization rate	number of dental amalgams, fish consumption, use of skin-lightening creams, and source of drinking water	Pregnancy outcome: 321 cases who did not achieve pregnancy vs. 203 controls who had successful pregnancy (as measured by a blood test); Fertilization outcome: 63 cases who did not achieve fertilization vs. 556 controls who produced fertilized eggs ; Single site	31.76 ± 5.12	1. Mean blood mercury level was 3.70 ± 3.55 (µg/L) and mean follicular mercury level was 2.48 ± 4.72 (µg/L); mercury levels ≥5.8 µg/L (the EPA safety limit) were found in the blood of 18.7% (n=90) and follicular fluid of 8.3% (n=51) of the women; 2. Blood mercury levels did not differ between pregnancy cases and controls (3.62 ± 3.08 vs. 3.82 ± 4.18; p=0.73) or between fertilization cases and controls (3.80 ± 3.59 vs. 3.69 ± 3.55; p=0.78); pregnancy controls (or women who did get pregnant) had higher follicular mercury levels than pregnancy cases (2.65 ± 3.54 vs. 2.12 ± 2.47; p=0.08) but follicular mercury levels did not differ between fertilization cases and	Using multiple linear regression analysis to identify potential predictors of mercury levels in blood and follicular fluid after controlling for various confounding variables: women's working status (p=0.01) use of skin-lightening creams (p=0.002) BMI (p=0.001) were the only predictors of blood mercury levels, number of dental amalgams (p=0.03) recent painting of the house (p=0.005), drinking coffee (p=0.0) women's working status (p=0.04) were associated with follicular mercury levels using correlation analysis, a positive relationship was found between mercury in blood and follicular fluid (r=0.25, p=0.0)	N/A	No mercury speciation was done. Urine mercury was not assessed

Authors Country	Study Design Number of Subjects	Type of mercury studied Type of measure	Mercury effects studied	Cofactors Evaluated	Comparison group Single vs. Multi-site	Mean age (years)	Primary endpoint findings	Secondary endpoint findings	Mean follow-up and follow-up rate	Limitations
							controls (2.38 ± 2.92 vs. 2.49 ± 4.88; p=0.79); 3. After backward elimination adjustment for various confounding variables, no effects of blood or follicular mercury were found on pregnancy or fertilization outcomes			
Palkovicova et al.[9] Slovakia	Cross-sectional; 99 mother-child pairs	Dental amalgam; Blood	N/A	Fish consumption	No Multi-site	25.7	1. Median Hg concentration values were 0.63 mg/l (range 0.14–2.9 mg/l) and 0.80 mg/l (range 0.15–2.54 mg/l) for maternal and cord blood, respectively. No cord blood Hg concentrations reached the level considered to be hazardous for neurodevelopmental effects in children exposed to Hg in utero (EPA reference dose for Hg of 5.8 mg/l in cord blood). 2. A significantly positive correlation between maternal and	No significant effect found between fish intake in pregnancy and maternal or cord blood Hg conc.		No mercury speciation done. Small sample size, exposure outcome not evaluated. Used self-reported information about dental filling

Authors Country	Study Design Number of Subjects	Type of mercury studied Type of measure	Mercury effects studied	Cofactors Evaluated	Comparison group Single vs. Multi-site	Mean age (years)	Primary endpoint findings	Secondary endpoint findings	Mean follow-up and follow-up rate	Limitations
							cord blood Hg concentrations (spearman's rho=0.79; p<0.001) was found 3. Bivariate analyses showed a positive association between the number of maternal fillings and the levels of Hg in the cord blood (r=0.46, P<0.001) and an inverse relationship between the levels of Hg in the cord blood and the number of years since the last filling (r=-0.37, <0.001). Associations remained significant after adjusting for maternal age and education.			
Yalcin et al.[11] Turkey	Prospective observational ; 44 mother-child pairs	Total mercury; Breast milk, blood	Effect on growth and development	Fish consumption, occupational exposure, smoking	No Single site	27.8	1. Breast milk Hg levels (mean conc. 3.42 ± 1.66µg/L) measured at 10-20 days post partum showed no affect on infant weight, length, head circumference or blood pressure in the 2 year period of study (p>0.05, n=21). 2. The		48% (21 of 44) at 2 years. 100% (all children) had Denver test at 5 months and 2 yrs post partum.	Small sample size, Single sample breast milk Hg was measured. Did not take into account variations

Authors Country	Study Design Number of Subjects	Type of mercury studied Type of measure	Mercury effects studied	Cofactors Evaluated	Comparison group Single vs. Multi-site	Mean age (years)	Primary endpoint findings	Secondary endpoint findings	Mean follow-up and follow-up rate	Limitations
							Denver test for infant development was normal for all children at 5 months' and 2 years' post partum regardless of milk Hg concentration. 3. Maternal anemia, active/passive smoking and offal intake (consumption of liver, brain of bovine or sheep) positively influenced milk Hg concentration (R2 =0.427, F=9.704, p<0.001 4. Breast milk Hg levels showed no correlation with number of amalgam filled teeth (mean 2.2±1.5, range 0-5, r=0.092; p>0.05).			in Hg level with time of day and feeding. Length of follow-up may be inadequate to observe impact of Hg effect. No placement or removal of amalgam fillings during pregnancy period
Geier et al.[12] U.S.	Case control; 100 qualifying participants born between 1990–1999 and diagnosed with DSM-IV autism	maternal dental amalgam; clinical assessment	Severity of autism	No	No Single site	10.4	Subjects whose mom with ≥6 amalgams during pregnancy were 3.2-fold significantly more likely to be diagnosed with autism (severe), in comparison to ASD (mild), than subjects with ≤5			No biologic measure of mercury. No cofactors examined.

Authors Country	Study Design Number of Subjects	Type of mercury studied Type of measure	Mercury effects studied	Cofactors Evaluated	Comparison group Single vs. Multi-site	Mean age (years)	Primary endpoint findings	Secondary endpoint findings	Mean follow-up and follow-up rate	Limitations
	(severe) or ASD (mild)						amalgams during pregnancy.			
Gerhardsson et al.[13] Sweden	Cross-sectional; 100 pregnant females	Total mercury; Blood and hair	No	Fish consumption, work exposure, chewing gum, smoking	No Multi-site	30	1. Blood mercury : 0.70 ug/L (0.27–2.1); Hair mercury: 0.22 (0.04–0.83) ug/g; average number of occlusal filling: 3 (0-14); all filling: 7 (0-48)	B-Hg was related to the number of occlusal amalgam fillings (multiple r =0.51; p < .001). The levels of mercury in whole blood were lower than suggested biological reference intervals.		No clinical outcomes assessed. Urine mercury not assessed.
Lygre et al.[14] Norway	Cohort; 67,355 pregnancies	Dental amalgam; number of amalgams	No	Smoking, alcohol use	No Multi-site	29.6	lower education, higher BMI, older age, smoking during pregnancy are factors associated with having 12 teeth or more with amalgam fillings.	mean number of teeth with amalgam: 4.9 (SD=4.1)	13 weeks, 75 %	No clinical outcomes assessed. No biologic measure of mercury.

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4 Table 2: Genetics

Authors Study (year) Country	Study Design Number of Subjects	Type of mercury studied Type of measure	Mercury effects studied	Cofactors Evaluated	Comparison group Single vs. Multi-site	Mean age (years)	Primary endpoint findings	Secondary endpoint findings	Mean follow-up and follow-up rate	Limitations
Echeverria et al.[13] U.S.	Cross-sectional; 164 male dentists and 101 female dental assistants practicing in Washington state	Total mercury; Urine	the effects of polymorphisms on susceptibility for specific neurobehavioral functions associated with mercury exposure in human subjects	No	No Single site	males: 48.8 ± 7.7; females: 36.0 ± 8.8	the outcome of interest was the interaction effect of urinary mercury concentration and the serotonin transporter gene-linked polymorphic region (5-HTTLPR) polymorphism on neurobehavioral and mood domains; 1. the mean urinary mercury (HgU in µg/L) for males dentists was 2.52 ± 2.22 and for female dental assistants was 1.98 ± 1.98; 2. evidence for an additive effect for urinary mercury and 5-HTTLPR polymorphism in both groups was observed for tests of Finger Tap Alternate and Hand Steadiness Factor1			There was no comparison group of individuals without occupational exposure to mercury.
Heyer et al[16] U.S.	Cross-sectional; 157 male dentists, 84 female assistants	Total mercury; Urine	5-HTTLPR polymorphism and 12 symptom groups/mood	smoking, alcohol use	No Single site	49 for male and 37 for female	both significant and consistent associations were observed between increased symptoms and the 5-HTTLPR polymorphism involving two copies of the short or "s" allele (full mutation), but not with the polymorphism involving only one copy (heterozygous), demonstrating a gene–dose relationship for symptom reporting.	no consistent associations were found between either urinary mercury concentration or the chronic index of mercury exposure and any		There was no comparison group of individuals without occupational exposure to mercury.

Authors Study (year) Country	Study Design Number of Subjects	Type of mercury studied Type of measure	Mercury effects studied	Cofactors Evaluated	Comparison group Single vs. Multi-site	Mean age (years)	Primary endpoint findings	Secondary endpoint findings	Mean follow-up and follow-up rate	Limitations
								category of symptoms		
Heyer et al.[17] U.S.	Cross-sectional; 396 dentists and dental assistants	Total mercury; Urine	COMT polymorphism and 12 symptom groups/mood	smoking, alcohol use	No Single site	48 for male and 36 for female	consistent and significant associations were found between increased symptoms and the COMT polymorphism involving the double allelic substitution (full mutation) compared to subjects with no substitutions	No consistent patterns of association between either urinary mercury concentration or the chronic index of mercury exposure and any category of symptoms were observed		There was no comparison group of individuals without occupational exposure to mercury.

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6 Table 3 Hypersensitivity/Immunology/Autoimmunity

Authors Study (year) Country	Study Design Number of Subjects	Type of mercury studied Type of measure	Mercury effects studied	Cofactors Evaluated	Comparison group Single vs. Multi-site	Mean age (years)	Primary endpoint findings	Secondary endpoint findings	Mean follow-up and follow-up rate	Limitations
Eyeson et al[18] England	Retrospective chart review; 56 consecutive patients specifically presenting with the belief that their oral/medical symptoms or conditions were caused by mercury toxicity from amalgam fillings	Dental amalgam; Urine and blood	the relationship between patient complaints of oral and medical symptoms related to perceived mercury toxicity from amalgam fillings and mercury levels in their blood and urine	No	No Single site, Multi dentist	N/A (the majority, or 62.5% were between ages 40 and 59, with 19.64% less than 40 years and 17.86% age 60 years or older)	1. presenting complaints included oral cavity symptoms (soreness, pain, metallic tasted, hypersalivation), neurological symptoms (memory loss, confusion, headaches and dizziness), musculoskeletal (joint ache, fatigue and malaise), and anxiety and depression; 2. mean blood mercury level was 19.9 ± 11.8 nmol/L and mean urine mercury level was 17.0 ± 11.6 nmol/L; the mean values were significantly lower than the normal threshold value for blood or urine mercury of 50 nmol/L; 3. all subjects reporting oral symptoms (n=27) were patch tested using the European Standard and Dental Material Series and 26 were found to have a negative response while 1 subject had a weak response to mercury amalgam; no patients were advised to have their metallic fillings replaced; 4. higher blood mercury levels were found in subjects with	1. in secondary analysis, the relationship between subgroups of co-morbidities and mercury levels was examined; blood mercury levels of 2 patients with multiple sclerosis (MS) was higher than those without MS (47.00 vs. 19.33, p=0.02) and urine levels of those reporting MS were higher as well (42.00 vs. 15.74, p=0.001); after adjustment for age and gender using multiple logistic regression, mercury levels in blood or urine were not significant for MS; 2. the relationship between number of amalgams and co-morbidities was also		There were no psychological measurements taken to examine perceived symptoms or amount of somatization.

Authors Study (year) Country	Study Design Number of Subjects	Type of mercury studied Type of measure	Mercury effects studied	Cofactors Evaluated	Comparison group Single vs. Multi-site	Mean age (years)	Primary endpoint findings	Secondary endpoint findings	Mean follow-up and follow-up rate	Limitations
							presenting complaints in the oral cavity (23.65 vs. 16.33, p=0.03); after adjustment for age and gender using multiple logistic regression, the blood mercury levels remained a positive significant factor for patients presenting with an oral complaint (adjusted OR=1.074, 95% CI= 1.005, 1.149, p=0.04); no other presenting complaint category was associated with blood or urine mercury; no presenting complaint categories were associated with number of amalgams; also, number of amalgams was not associated with blood or urine mercury	assessed, and previously diagnosed autoimmune disease was more common in the group with >10 amalgams (26.3%) versus those with 6-10 amalgams (5.6%) or 0-5 amalgams (0%), p=0.03; after adjustment for age and gender, number of amalgams was not associated with auto-immune disorders		
Shenker et al[19] U.S.	Exploratory substudy; 59 children	Dental amalgam; Blood, urine	Immunotoxicity		Amalgam group vs. composite group	Amalgam group-8.1 Composite group-8.0	1. The mean number of tooth surfaces restored during the five-year period was 7.8 for amalgam group and 10.1 for composite group. 2. No consistent or statistical significant difference observed between treatment groups in terms of lymphocytes, monocytes and neutrophils distribution by		Amalgam group-20 at 5 years; 29 included in primary analyses,	limited statistical power: small sample size and lack of existing knowle

Authors Study (year) Country	Study Design Number of Subjects	Type of mercury studied Type of measure	Mercury effects studied	Cofactors Evaluated	Comparison group Single vs. Multi-site	Mean age (years)	Primary endpoint findings	Secondary endpoint findings	Mean follow-up and follow-up rate	Limitations
							graphical evaluation or ANCOVA models. 3. In the amalgam group, a slight but non statistical significant decline in responsiveness of T cells was observed at 5 to 7 days after amalgam treatment. No difference was observed between treatment groups for proliferative responses of T or B cells across time. 4. Monocytes in the amalgam group exhibited reduce response within 5 to 7 day after treatment. Neutrophils fluctuated within and between groups but none of these was statistically significant.		Composite group-23 at 5 years; 30 included in primary analysis.	dge on effect of Hg on immune system limited the range of cell function assessed. As an exploratory study, interpretation can only be based on observation of trends and not significant

Authors Study (year) Country	Study Design Number of Subjects	Type of mercury studied Type of measure	Mercury effects studied	Cofactors Evaluated	Comparison group Single vs. Multi-site	Mean age (years)	Primary endpoint findings	Secondary endpoint findings	Mean follow-up and follow-up rate	Limitations
										difference.
Pezelj-Ribaric et al[20] Croatia	Comparative; 40	Dental amalgam;	Oral lichenoid reaction (OLR)	No	Cases: 20 patients with OLR, Controls: 20 healthy volunteers.	Cases 50 ± 9, Control group 51 ± 9.	1. Sixteen of 20 study patients whose amalgam fillings were replaced with fillings based on composite resin, gold , porcelain or combination of these showed complete healing of OLR, 3 patients had marked improvement; 1 patient showed no improvement. 2. In the amalgam group, levels of IL-6 and IL-8 measured before replacement were significantly higher than after replacement, p=0.003 and p<0.001 respectively. Levels IL-6 and IL-8 measured before and after intervention in control subjects did not differ significantly, p= 0.226 and 0.199 respectively. 3. Filling replacement in the amalgam group lowered the pro-inflammatory cytokines values to levels that correspond to those of control group.	Sixteen of 20 (80%) patch-tested patients showed sensitization to inorganic mercury.	2 months to 3.5 years	Unclear if any of the control group had dental amalgam fillings. Small sample size.
Guzzi et al[21]	Cross-sectional;	Dental amalgam;	increase of serum levels of	fish consumption,	No Single site	45	None of the patients showed evidence of anti-GBM autoimmunity either in subgroups			Small sample size.

Authors Study (year) Country	Study Design Number of Subjects	Type of mercury studied Type of measure	Mercury effects studied	Cofactors Evaluated	Comparison group Single vs. Multi-site	Mean age (years)	Primary endpoint findings	Secondary endpoint findings	Mean follow-up and follow-up rate	Limitations
Italy	24 patients with long-history of dental amalgam		antibodies to anti-GBM-IgG	vaccination coverage			with strong allergy to mercury or its compounds (i.e., organic mercury) or in those patients who had past thimerosal-containing vaccine coverage.			

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9 **Table 4: Children**

Authors Study (year) Country	Study Design Number of Subjects	Type of mercury studied Type of measure	Mercury effects studied	Cofactors Evaluated	Comparison group Single vs. Multi-site	Mean age (years)	Primary endpoint findings	Secondary endpoint findings	Mean follow-up and follow-up rate	Limitations
Barregard et al.[24] U.S.	Secondary analysis of RCT; 534 children aged 6-10 years	Dental amalgam; Urine, corrected for creatinine	treatment group effects on markers of glomerular and tubular kidney function: urinary excretion of albumin, alpha-1-microglobulin (A1M), γ-glutamyl transpeptidase (γ-GT), and N-acetyl-β-D-glucosaminidase (NAG)	No, because treatment groups were randomized	Random assignment to treatment group (dispersed phase amalgam vs. resin composite material) was used to restore all posterior teeth with caries at baseline and incident caries during the 5-year trial Multi-site	7.9 ± 1.4	children with diabetes and other kidney disease, as well as elevated γ-GT at baseline, were excluded from analyses; 1. no significant differences between treatment groups in average levels of renal biomarkers were found in controlled models; also, no significant effects of number of dental amalgams on the renal biomarkers were found; 2. no significant effects of urine mercury levels on the renal biomarkers were found	there was a significantly increased prevalence of microalbuminuria (MA , urinary albumin > 30 mg/g creatinine) found among children in the amalgam group in years 3–5 (adjusted odds ratio 1.8; 95% confidence interval, 1.1–2.9) than in the composite group; 10 children in the amalgam group had MA in both years 3 and 5, versus 2 children in the composite group (p = 0.04, Fisher's Exact test); it is unknown if these children will have persistent MA, or if the MA is	81%	The trial has low power to detect an effect that occurs only in a small susceptible fraction of children. Also, urine samples were stored frozen until analysis

Authors Study (year) Country	Study Design Number of Subjects	Type of mercury studied Type of measure	Mercury effects studied	Cofactors Evaluated	Comparison group Single vs. Multi-site	Mean age (years)	Primary endpoint findings	Secondary endpoint findings	Mean follow-up and follow-up rate	Limitations
								reversible (temporary); there was no significant increase in MA with increasing number of amalgam fillings (p=0.30) or urine mercury excretion (p=0.71); however when an interaction term between blood lead and urinary mercury was included in the model, it was statically significant in year 5 (p=0.02) and borderline significant in years 3-5 (p=0.07)		
Bellinger et al[26] U.S.	Secondary analysis of RCT; 534 children aged 6-10 years	Dental amalgam; Creatinine corrected urine	treatment group effects on the psychosocial health of children	No, because treatment groups were randomized	Random assignment to treatment group (dispersed phase amalgam vs. resin	7.9 ± 1.4	primary psychosocial outcome was score on the parent-completed Child Behavior Checklist (CBCL) done at baseline and 5 years; treatment groups were compared in terms of the change in CBCL scores over time, adjusted for various	secondary outcomes were children's self-reports on the Behavior Assessment System for Children (BASC-SR) done at 5 years (n=426);	395/534 (74.0%)	For the current study, the available sample size of 395 children provided 80% power

Authors Study (year) Country	Study Design Number of Subjects	Type of mercury studied Type of measure	Mercury effects studied	Cofactors Evaluated	Comparison group Single vs. Multi-site	Mean age (years)	Primary endpoint findings	Secondary endpoint findings	Mean follow-up and follow-up rate	Limitations
					composite material) Multi-site		confounding variables (n=395); 1. all significant group differences actually favored the amalgam group, and included greater improvement in areas of Internalizing, Total problem behaviors, the competence subscale of Activities, and two behavior subscales of Anxious/Depressed and Delinquent behaviors; 2. mean urinary mercury excretion between years 3 and 5 of follow-up was not significantly associated with any CBCL global score	1. the scores of children in both treatment groups were similar and all significant associations again favored the amalgam group including better scores on the Emotional Symptoms Index and Personal Adjustment; urinary mercury excretion was not examined with BASC-CR scores		at p<0.05 to detect a difference of 0.2 points between treatment groups in the primary outcome.
Ye et al[25] China	Comparative; 198 children ages 7-11 years	Total mercury; Urine	Nephrotoxicity, Neurobehavioral and Neuropsychological performance	Fish consumption & other factors	Amalgam group- 198, No Amalgam group (Referent) - 205 Multi-site	Amalgam group - 9.9 ± 0.7, Referent group- 9.8± 0.8	1. The geometric mean level of urinary mercury was 15% higher in children with amalgam group (1.6 mg/g Cr) than in the children without group (1.4 mg/g Cr), but this difference was not statistically significant (p=0.11). 2. Logistic regression analysis showed no associations between amalgam exposure		N/A	Short mercury exposure time (median amalgam exposure time 31 months) may be insufficient

Authors Study (year) Country	Study Design Number of Subjects	Type of mercury studied Type of measure	Mercury effects studied	Cofactors Evaluated	Comparison group Single vs. Multi-site	Mean age (years)	Primary endpoint findings	Secondary endpoint findings	Mean follow-up and follow-up rate	Limitations
							and risk of microalbuminuria or high NAG activity after controlling confounders (age, sex, family income, fish consumption, parent education and grade). Children with and without amalgam fillings had similar adjusted levels of NAG activity and ALB in multiple regression models 3. Children with and without amalgam fillings had similar adjusted scores on neurobehavioral and neuropsychological tests. 4. No difference in IQ or school performance was found between the two groups.			time to detect effect. Insufficient statistical power to detect effect due to small sample size and small number of amalgam fillings
Surkan et al.[28] U.S.	Registry; 355 children ages 6-10 years	Methyl mercury; Hair	Neuropsychological effects	Fish consumption	No Multi-site		1. No significant linear relationships were observed between hair Hg level and the neuropsychological test scores in adjusted analyses. This result is unaffected by addition of fish consumption in the model.			Large fraction of the sample's hair Hg was computed because MeHg levels

Authors Study (year) Country	Study Design Number of Subjects	Type of mercury studied Type of measure	Mercury effects studied	Cofactors Evaluated	Comparison group Single vs. Multi-site	Mean age (years)	Primary endpoint findings	Secondary endpoint findings	Mean follow-up and follow-up rate	Limitations
							2. Significant departures from linearity were observed in the relationships between hair Hg level and two test scores, WIAT Math Reasoning score and WRAMVA Visual-Motor Composite (p = 0.03 for both). For both test scores, the relationship was positive at hair Hg levels below 0.5 µg/g and inverse between 0.5 and 1.5µ g/g. 3. Test scores of children with hair Hg levels >1.0 µg/g appeared to be lower than those of children with levels <1.0 mg/g, but few children had levels in this upper range and these differences did not reach statistical significance. 4. Hair Hg levels below 1 .0 µg/g in US school-age children were not adversely related to neuropsychological function.			were below detection.
Woods et al[23] Portugal	RCT; 479 children aged 8-12	Dental amalgam; urine	Renal toxicity	No	Composite vs. amalgam	Amalgam 10.2yrs, Compos	1. Mean urinary Hg concentrations in the amalgam group increased to a peak of 3.2 µg/g at yr 2, then slowly declined to near			1. Small sample size for 8-9 yr old group (n=195) in

Authors Study (year) Country	Study Design Number of Subjects	Type of mercury studied Type of measure	Mercury effects studied	Cofactors Evaluated	Comparison group Single vs. Multi-site	Mean age (years)	Primary endpoint findings	Secondary endpoint findings	Mean follow-up and follow-up rate	Limitations
	years at baseline					ite 10yrs	baseline levels by yr 7 of follow-up. No changes in the mean urinary Hg levels were observed in the composite group during the 7-yr follow-up period. 2. No effects of amalgam treatment on the mean concentrations of uro- (8-carboxyl), hepta- (7-carboxyl), or hexa- (6-carboxyl) porphyrins were observed when treatment groups were compared. However, incipient increases in the mean concentrations of penta-, precopro-, and coproporphyrins occurred in the amalgam-treated subjects, especially in the 8-9 year olds that is most apparent during yr 2 through 3 yr of follow up, the period of highest mercury exposure from amalgam treatment. These changes were not statistically significant when compared with composite group.			whom incipient increases in treatment - specific porphrins (penta, precopro and coproporphyrin) was observed could have limited the study's power to detect a difference. Study had low follow-up rate at 7 years.

Authors Study (year) Country	Study Design Number of Subjects	Type of mercury studied Type of measure	Mercury effects studied	Cofactors Evaluated	Comparison group Single vs. Multi-site	Mean age (years)	Primary endpoint findings	Secondary endpoint findings	Mean follow-up and follow-up rate	Limitations
							3. Renal Hg concentration associated with incipient increases in urinary porphyrins was estimated to be 2.7µg/g renal cortex (based on group mean amalgam filling of 17.8) which corresponds to mean urine excretion of 3.2µg/g creatinine. This value is about 5 folds less than that at which renal damage is estimated to occur in children.			
Woods et al[22] Portugal	RCT; 507 children ages 8-12	Dental amalgam; urine	Renal injury	No	Composite resin vs. amalgam Multi-site		1. GST-α concentrations are similar between treatment groups and in each sex and race (white vs. non white) group. 2. GST-π levels tended to increase over the course of study by four to six- fold from 9-18 years of age. This increase was seen across all groups irrespective of treatment group, race or gender. There was no significant difference in any of the parameters between treatment groups. Females			Adjusted for group difference at baseline that may have occurred despite randomization.

Authors Study (year) Country	Study Design Number of Subjects	Type of mercury studied Type of measure	Mercury effects studied	Cofactors Evaluated	Comparison group Single vs. Multi-site	Mean age (years)	Primary endpoint findings	Secondary endpoint findings	Mean follow-up and follow-up rate	Limitations
							had GST-π almost twice as those of males ($p < 0.00001$). 3. Albumin concentrations were constant throughout the follow-up period and did not differ by treatment. Females had 39% higher albumin than males($p<0.00001$). 4. No significant effect of amalgam treatment on proportion of children with microalbuminuria (>30 mg/g creatinine).			
Woods et al[29] U.S.	Exploratory; 197 children ages 2-12 years	N/A Urine	Nephrotoxicity	Fish meals per week during pregnancy, Vaccination-total number of vaccinations and vaccinations prior to 2002, chelation history	Three groups: Neurotypical (NT), Autistic (AU) and pervasive developmental disorder-not otherwise specified (PDD-NOS).	Males 6.19± 2.67, Females 6.86 ±3.00	1. Mean concentration of most urinary porphyrins, particularly uro, hepta, and coproprphins are high in younger children and decline by as much as 2.5-fold between 2 and 12 years of age. 2. Among males in the 2- to 12-year age groups, the mean concentrations of hexacarboxyl- ($p < 0.01$), pentacarboxyl- ($p < 0.001$), and copro- ($p < 0.009$) porphyrins were significantly higher among AU compared			Small sample size for NT and AU subjects may not have enough power to detect difference. Exposure to other environmental sources e.g. occupation were not

Authors Study (year) Country	Study Design Number of Subjects	Type of mercury studied Type of measure	Mercury effects studied	Cofactors Evaluated	Comparison group Single vs. Multi-site	Mean age (years)	Primary endpoint findings	Secondary endpoint findings	Mean follow-up and follow-up rate	Limitations
							with NT groups by ANOVA F test values. In contrast mean Uro- and precoproporphyrins concentrations are comparable between NT and AU children of the same age ranges. 3. No differences were found between NT and AU in urinary Hg levels or in past Hg exposure determined by fish consumption, number of dental amalgam fillings, or vaccines received in total , or before 2002.			assessed and controlled for.
Lauterbatch et al.[27] Portugal	RCT; 507 children aged 8 through 12 years	Dental amalgam; Clinical assessment	Neurological effects, including an evaluation of neurological hard signs (NHSs), presence of tremor and	no difference on vaccination history, dietary mercury intake.	amalgam vs. resin-based composite Single school district	10.1	no significant differences between treatment groups in any of the neurological measures		55%	

Authors Study (year) Country	Study Design Number of Subjects	Type of mercury studied Type of measure	Mercury effects studied	Cofactors Evaluated	Comparison group Single vs. Multi-site	Mean age (years)	Primary endpoint findings	Secondary endpoint findings	Mean follow-up and follow-up rate	Limitations
			neurological soft signs (NSSs).							

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12 **Table 5 Number of Amalgams/Removal**

Authors Study (year) Country	Study Design Number of Subjects	Type of mercury studied Type of measure	Mercury effects studied	Cofactors Evaluated	Comparison group Single vs. Multi-site	Mean age (years)	Primary endpoint findings	Secondary endpoint findings	Mean follow-up and follow-up rate	Limitations
Rothwell et al. [36] U.K.	Cross-sectional; 39 women	Dental amalgam; Clinical assessment	Ototoxicity	Fish consumption, past smoking, noise exposure evaluated.	Composite (non amalgam)	42.5	1. An increase in the number of amalgams (range 0 to 16, mean 7.1) was associated with poorer auditory thresholds at 8, 11.2, 12.5, 14, and 16 kHz. Strongest association was at 14 Hkz (n= 39, p<0.001, r2 = 0. 35, F 19.5), where each amalgam was associated with a 2.4 dB decline in hearing threshold (95% CI 1.3-3.5 dB), independent of socioeconomic factors. 2. No sig correlation was found between number/scores of composite fillings or drilling episodes and auditory thresholds.			Small sample size. Participants are of similar age with variable amount of amalgam fillings. It is unclear how study subject were categorized given that participants had a mixture of amalgam and composite fillings.
Weidenhammer et al.[32] Germany	Secondary analysis of RCT; 78	Total mercury; Blood and urine	Subject symptoms, psychologi	None	Amalgam Removal group-55, Health	35	1. Patients had slightly reduced extraversion and slightly elevated emotionality instability (personality traits)		100%	Symptom reduction could be due to temporal

Authors Study (year) Country	Study Design Number of Subjects	Type of mercury studied Type of measure	Mercury effects studied	Cofactors Evaluated	Comparison group Single vs. Multi-site	Mean age (years)	Primary endpoint findings	Secondary endpoint findings	Mean follow-up and follow-up rate	Limitations
			cal distress		promotion no Removal -23		compared with norm samples prior to intervention 2. In both treatment groups, patients' subjective symptoms decreased after intervention but no statistically significant difference was found between the two groups. 3. The decrease in mercury levels after intervention was closely associated with removal of amalgam fillings (r = 0.64 in regression analysis). 4. Higher mercury levels were associated with higher subjective symptom scores before the intervention (r = 0.25-0.39), and reductions in mercury levels after the intervention were associated with decrease in subjective symptom scores (r = 0.24-0.42). 5. Mercury levels did not significantly correlate with psychological distress (r = 0.05-0.25) and health related quality of life (r = -0.03-0.18).			relief due to short follow up period of this study. Patients investigated may not be true representation of amalgam patients with symptoms seeking relief since study patients had to accept amalgam not being removed. Therefore difficult to generalize the findings of this study.

Authors Study (year) Country	Study Design Number of Subjects	Type of mercury studied Type of measure	Mercury effects studied	Cofactors Evaluated	Comparison group Single vs. Multi-site	Mean age (years)	Primary endpoint findings	Secondary endpoint findings	Mean follow-up and follow-up rate	Limitations
Halbach et al[30] Germany	RCT; 91 adult patients with dental amalgam fillings and health complaints;	Total mercury; Blood and urine		Dietary coexposure	(A) removal of the fillings; (B) removal and non-specific detoxification, and (C) a health promotion program without removal.	20-50	After amalgam removal, inorganic Hg dropped rapidly in plasma and red cells, stabilizing at 27% of preremoval levels after 60 days. Concentrations of organic Hg in plasma remained unchanged. Urinary concentration and excretion of total-Hg were very similar to those of inorganic-Hg levels in plasma.		81%	
Barregard et al. [34] Sweden	Cross-sectional; 109 living kidney donors, 60 women and 49 men	Total mercury; Fresh kidney cortex sample	No	Diet variables (fish and water supply) and occupational exposure	No Single site	Median =51 (range 24-70)	1. the mean kidney mercury concentration was 0.32 µg/g with a median of 0.21 µg/g; 2. kidney mercury levels increased with total number of amalgam fillings (r=0.62, p<0.001); 3. in multiple linear regression analysis, log kidney mercury was positively and significantly associated with the total number of amalgam surfaces(p<0.001), but not with age, sex, weight, or fish consumption; 4. Kidney mercury increased by about 6% with every additional amalgam surface.	The kidney mercury concentration was higher in women (median of 0.25) than men (median of 0.18) but the difference was not statistically significant. This could be due to the fact that the female kidney is smaller.		The study did not speciate mercury; if metal concentrations are not uniform within the kidney cortex, results are not precise; also, kidney donors represent a healthy part

Authors Study (year) Country	Study Design Number of Subjects	Type of mercury studied Type of measure	Mercury effects studied	Cofactors Evaluated	Comparison group Single vs. Multi-site	Mean age (years)	Primary endpoint findings	Secondary endpoint findings	Mean follow-up and follow-up rate	Limitations
										of the population.
Fakour et al. [35] Iran	Cross-sectional; 82 healthy women, with absence of known occupational and/or environmental exposure to mercury	Total mercury; Hair and saliva	No	All participants had the same fish consumption patterns (<3 times/month) and therefore this variable was constant.	Three groups by number of amalgam fillings: i) no amalgam fillings (n=20), ii) 1-4 amalgam fillings (n=30), and iii) >4 amalgam fillings (n=32)	29.37 ± 8.12	1. the mean mercury concentration in hair was 1.28 µg/g and the mean mercury concentration in saliva was 4.14 µg/l; mercury concentration in saliva samples were significantly higher than hair samples (p<0.001); 2. there was a significant difference (p<0.001) for both hair and saliva mercury concentration by amalgam groups, with women with no amalgam fillings having the lowest mercury concentrations and women with >4 amalgam fillings having the highest mercury concentrations; 3. number of amalgam fillings was highly correlated with both hair (r=0.94, p<0.001) and saliva (r=0.93, p<0.001) mercury concentrations in these women	there was a strong positive correlation between the mercury concentration in hair and in saliva (p=0.89, p<0.001)		This study did not speciate mercury and did not measure other potential sources of mercury exposure such as cosmetic materials (i.e. skin-lightening cream)
Masereji an et al[33]	Cohort;	Total mercury;	No	Fish consumptio	No	11.5	the current total of amalgam surfaces was the most robust		81%	

Authors Study (year) Country	Study Design Number of Subjects	Type of mercury studied Type of measure	Mercury effects studied	Cofactors Evaluated	Comparison group Single vs. Multi-site	Mean age (years)	Primary endpoint findings	Secondary endpoint findings	Mean follow-up and follow-up rate	Limitations
U.S.	267 children who were assigned to the amalgam treatment group in New England Children's Amalgam Trial	Urine		n, chew gum frequency, teeth grinding, teeth brushing	Multi-site		predictor of current U-Hg, whereas posterior occlusal surface-years was best for cumulative U-Hg.			
Melchart et al. [37] Germany	Non-experimental; 81 subjects	Total mercury; Blood, urine, and saliva	No	No	patients complaining about health problems attributed to amalgam vs. healthy volunteers with amalgam fillings vs. healthy amalgam-free volunteers.	40 for group A, 28 for group B and 23 for group C	The concentrations of inorganic mercury in erythrocytes and plasma as well as of total mercury in plasma, were significantly higher in groups A and B than in group C. However, there were no significant differences between groups A and B. The same is for urine and saliva total mercury. Levels of organic Hg were equal in all groups. Urine Hg levels		100%	

Authors Study (year) Country	Study Design Number of Subjects	Type of mercury studied Type of measure	Mercury effects studied	Cofactors Evaluated	Comparison group Single vs. Multi-site	Mean age (years)	Primary endpoint findings	Secondary endpoint findings	Mean follow-up and follow-up rate	Limitations
							tended to correlate better with blood than with saliva .			

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15 **Table 6 Occupational Exposure**

Authors Study (year) Country	Study Design Number of Subjects	Type of mercury studied Type of measure	Mercury effects studied	Cofactors Evaluated	Comparison group Single vs. Multi-site	Mean age (years)	Primary endpoint findings	Secondary endpoint findings	Mean follow-up and follow-up rate	Limitations
deOliveira et al.[38] Brazil	Quasi-experimental, pretest/post-test; 20 subjects divided into two groups; Group 1 (n=10) were undergraduate students in dental school; Group 2 (n=10) were randomly chosen patients who needed replacement of	Dental amalgam; Creatinine corrected urine	the effect on patients and dental students as a result of a single manipulation of dental amalgam	None	No comparison groups for unexposed measurement Single site	Group 1 (dental students): 19-21 years; Group 2 (patients): 20-35 years	1. an increase in urinary mercury levels occurred in all sampled subjects; however, all results were below the biologic limit for individuals occupationally exposed proposed by WHO (≤5 µg/g creatinine); 2. there was a statistically significant difference in Group 1 (dental students) in mean urinary mercury levels (µg/g creatinine) from before and after their first working contact with dental amalgam (0.63 ± 0.13 vs. 0.84 ± 0.20; p=0.0038) and in Group 2 (patients) from before and after removal of amalgam restorations (0.55 ± 0.22 vs. 1.91 ± 0.38; p=0.0045)			This study did not examine any potentially confounding factors that could account for the acute increase in mercury levels (i.e. fish consumption, medicines, cosmetics, etc).

Authors Study (year) Country	Study Design Number of Subjects	Type of mercury studied Type of measure	Mercury effects studied	Cofactors Evaluated	Comparison group Single vs. Multi-site	Mean age (years)	Primary endpoint findings	Secondary endpoint findings	Mean follow-up and follow-up rate	Limitations
	dental amalgam restorations									
Farahat et al. [41] Egypt	Cross-sectional; 39 dental staff 42 control subjects selected from medical and nursing staff in a hospital,	Dental occupational exposure; Urine (creatinine corrected) and blood	the effect of mercury on thymus gland hormone level (thymulin)	amount of fish consumption/week	Control group (hospital staff) were chosen to match the exposed group (dental staff) in terms of age, sex, socioeconomic status, amount of dental fillings, and amount of fish consumption/ week	exposed group mean age 43.23 ± 10.75; control group mean age 41.33 ± 10.78	1. the exposed group and control group were not statistically different in terms of age, amount of dental fillings, and amount of fish consumption; 2. mean urinary mercury levels (µg Hg/g creatinine) were significantly higher ($p<0.001$) in the exposed workers (19.76 ± 1.37) than in the controls (5.44 ± 1.18); mean blood mercury levels (µg/L) were also significantly higher ($p<0.001$) in the exposed group (7.82 ± 0.97) than in the controls (4.82 ± 0.75); 3. there was no difference in kidney function between the	plasma nitrites and nitrates were also assessed to verify the effect of mercury on the L-arginine nitric oxide (NO) pathway as a possible mechanism of its immunotoxicity; 1. blood nitrite and nitrate levels were significantly lower among		The sample size was not large enough to stratify by variables such as gender and age.

Authors Study (year) Country	Study Design Number of Subjects	Type of mercury studied Type of measure	Mercury effects studied	Cofactors Evaluated	Comparison group Single vs. Multi-site	Mean age (years)	Primary endpoint findings	Secondary endpoint findings	Mean follow-up and follow-up rate	Limitations
							two groups, with both groups having similar mean values of blood urea and serum creatinine; 4. mean total blood thymulin hormone was significantly lower among dental workers than controls ($p<0.001$); depression in thymulin hormone level is a marker of subclinical immunosuppression	dental workers ($p<0.001$) compared to controls; therefore, the nitric oxide pathway is a possible mechanism for the impact of mercury on thymus gland function; 2. among the dental staff, duration of work was positively and significantly correlated with urinary mercury ($r=0.60$, $p<0.001$)		

Authors Study (year) Country	Study Design Number of Subjects	Type of mercury studied Type of measure	Mercury effects studied	Cofactors Evaluated	Comparison group Single vs. Multi-site	Mean age (years)	Primary endpoint findings	Secondary endpoint findings	Mean follow-up and follow-up rate	Limitations
								and blood mercury (r=0.51, p<0.001)		
Moen et al. [38] Norway	Cross-sectional; 41 dental assistants, 64 assistant nurses	Mercury vapor; Clinical assessment	Neurological and psychological effects	alcohol consumption, current smoking	dental assistants vs. assistant nurses	57	reported significant higher occurrence of neurological symptoms; psychosomatic symptoms, problems with memory, concentration, fatigue and sleep disturbance, but not for mood.			
Jaorsinska et al. [42] Poland, Sweden, Italy	Cross-sectional; 757 general population and CA workers	Metallic mercury; Urine	Renal function	fish consumption, occupational exposure to chloralkali	No Multi-site	21-44	Dental amalgam, chewing on amalgam, and fish consumption were positively associated with U-HgC. U-HgC is higher in women	In men, U-HgC was positively associated with the kidney markers, especially with NAG, but to some extent also with A1M and albumin.		

Authors Study (year) Country	Study Design Number of Subjects	Type of mercury studied Type of measure	Mercury effects studied	Cofactors Evaluated	Comparison group Single vs. Multi-site	Mean age (years)	Primary endpoint findings	Secondary endpoint findings	Mean follow-up and follow-up rate	Limitations

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18 **Table 7 Other**

Authors Study (year) Country	Study Design Number of Subjects	Type of mercury studied Type of measure	Mercury effects studied	Cofactors Evaluated	Comparison group Single vs. Multi-site	Mean age (years)	Primary endpoint findings	Secondary endpoint findings	Mean follow-up and follow-up rate	Limitations
Diez et al. [44] Italy	Cross-sectional; 237 dental clinic patients,	Total mercury; Hair	No	frequency of fish consumption	Three groups: i) amalgam and no fish group (n=98) that have dental amalgams and eat no fish, ii) no amalgam and fish group (n=62) that have no dental amalgams but eat fish, and (iii) amalgam and fish group (n=77) that have dental amalgams and eat fish Multi-site	39.9 ± 2.6	1. from the three comparison groups, the hair mercury concentration was significantly higher among those that have dental amalgams and eat fish (0.82 µg/g) compared to those with no amalgam but eat fish (0.69 µg/g) and those that have dental amalgam and eat no fish (0.46 µg/g); 2. in multiple linear regression analysis, gender, age, number of amalgam fillings and fish consumption were significantly associated with increased total mercury in hair but the predictor variable of fish consumption had the largest partial correlation; 3. Overall, it may be concluded that individuals who eat fish and have amalgam fillings have higher levels of total mercury than the other two comparison groups	1. overall, men had higher mean hair mercury concentrations than women (0.71 µg/g versus 0.56 µg/g, p=0.003) even though there were no significant differences between genders for age, frequency of fish consumption, and number of amalgam; 2. overall, there was no difference in hair mercury concentrations between those with amalgam fillings (n=175, mean=0.62 µg Hg/g) and those without amalgam fillings (n=62, mean=0.69 µg Hg/g), p=0.27; however, significant differences in hair mercury were found between the groups that eat fish or do not eat fish (0.76		This study did not speciate mercury; the age range of participants is limited and therefore results are not generalizable to the adult population

Authors Study (year) Country	Study Design Number of Subjects	Type of mercury studied Type of measure	Mercury effects studied	Cofactors Evaluated	Comparison group Single vs. Multi-site	Mean age (years)	Primary endpoint findings	Secondary endpoint findings	Mean follow-up and follow-up rate	Limitations
								µg/g versus 0.46 µg/g, p<0.05); 3. overall, there was a positive correlation between the consumption of fish and total mercury (r=0.536; p<0.05)		
Dunn et al. [45] U.S.	Secondary analysis of RCT; 534 children 6-10 years of age	Total mercury; Hair and urine (creatinine corrected)	No	Data collected annually from primary caregivers on dietary habits including fish consumption and gum chewing.	No Multi-site	7.9 ± 1.4	1. over the 5-year study period, the mean values for hair mercury were 0.3-0.4 µg/g and mean values for urine mercury were 0.7-0.9 µg/g creatinine; 2. repeated measures models were fit to determine significant predictors of hair and urine mercury using a backward elimination procedure; significant predictors of higher hair mercury across all study years included frequency of fish consumption, the Boston site (vs. Maine), and being of "other" race (other than black, white, or Hispanic); significant predictors of urine mercury across study years 3-5 included number of	to examine combined effects of fish consumption and amalgam exposure on hair and urine mercury, models were fit to include interaction terms; however, no significant interactions were found	313 children with all four years of hair mercury measurements and 343 children with all three years of urine mercury measurements	This study did not speciate mercury; children met the eligibility criteria for the trial and therefore this cohort is not a representative sample of all children

Authors Study (year) Country	Study Design Number of Subjects	Type of mercury studied Type of measure	Mercury effects studied	Cofactors Evaluated	Comparison group Single vs. Multi-site	Mean age (years)	Primary endpoint findings	Secondary endpoint findings	Mean follow-up and follow-up rate	Limitations
							amalgam fillings and use of chewing gum with amalgam fillings			
Mortazavi et al. [43] Iran	Cohort; 44	Total mercury; Saliva	release of mercury from dental amalgam	No	pre-/after MRI; use mobile phone vs. not Multi-site	30.7	1. saliva Hg concentrations of the patients before and after MRI were 8.6±3.0 and 11.3±5.3 Ilg L-',respectively (p<0.0l). 2. The mean±SE urinary Hg concentrations of the students who used mobile phones were 2,43±0.25, 2.71±0.27, 3.79±0.25, 4.8±0.27 and 4.5±O.32 Ilg L-, before the amalgam restoration and at days 1,2, 3 and 4, respectively. Whereas the respective Hg concentrations in the controls, were 2.07±0.22, 2.34±0.30, 2.51±0.25, 2.66±0.24 and 2.76±0.32).lg L-1.			

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Appendix 2: 2012 and 2014 FDA Updates to the Systematic Assessment of Peer Reviewed Epidemiologic Literature

2012 Assessment

Purpose

The purpose of this memorandum is to present the systematic literature review on risks associated with mercury (Hg) exposure from dental amalgam fillings for three sensitive groups:

(1) Pregnant women and their developing fetuses
(2) Children under six years of age
(3) Women who are breastfeeding and nursing infants

Background/Objective

Dental amalgam is a dental restorative material used to fill cavities caused by tooth decay. It is a heterogeneous inter-metallic compound, consisting of elemental Hg (liquid) and amalgam alloy (powder) composed of primarily silver, tin, and copper. Approximately 50% of dental amalgam is elemental Hg by weight. Dental amalgam has been on the U.S. market in its present form since the 1890s and has been the predominant and clinically preferred material for restoring most posterior teeth (i.e., molars and premolars) [1].

Dental amalgam is a "pre-amendment device," which means that it was in use prior to May 28, 1976 when the FDA was given broad authority to regulate medical devices by law. The law required the FDA to issue regulations classifying pre-amendment devices according to their risk into class I, II, or III. The two components of dental amalgam, dental Hg and amalgam alloy, were initially classified separately as Class I and Class II devices, respectively, in 1987. Overtime, there have been increasing concerns about Hg toxicity because the Hg vapor emitting from amalgam restorations can be absorbed by the patient through inhalation, ingestion, or other means [2]. To address these concerns, the Department of Health and Human Services (HHS), specifically U.S. Public Health Service (USPHS) and the Food and Drug Administration (FDA), evaluated the relevant scientific literature regarding the health effects of dental amalgam and published their findings in the 1993 and 1997 USPHS Reports on Dental Amalgam [3, 4]. Scientists and health professionals from U.S. government agencies (CDC, EPA, NIEHS, NIDR, NIOSH, and FDA) and academia with diverse science backgrounds and expertise in toxicology, neurotoxicology, immunotoxicology, and epidemiology, contributed to the literature review for these two reports. These two reports concluded similarly that "current body of data does not support claims that individuals with dental amalgam restorations will experience adverse effects, including neurologic, renal or developmental effects, except for rare allergic or hypersensitivity reactions".

These reports also recommended a strategic plan for USPHS agencies for future research, education, and regulation of dental amalgam including, particularly, FDA was recommended to regulate elemental Hg and dental alloy as a single product, and to require manufacturers to disclose the ingredients of these materials in product labeling.

Milestones on FDA regulations related to dental amalgam or dental products, were as follows:

(1) 1993-94 – Multiple Dental Products Panels:
- discussed the risks and benefits of dental amalgam,
- stated that there were no major risks associated with encapsulated amalgam, when used as directed, but recognized there was a small population of patients who may experience allergic reactions to the materials in the device, and
- recommended FDA reclassify the components of dental amalgam into a single class II regulation

(2) August 2006 -- A joint committee of CDRH Dental Products Panel and CDER Peripheral and Central Nervous System Drugs Advisory Committee:
- discussed FDA's draft White Paper on the latest peer-reviewed literature on dental amalgam,
- identified gaps in the scientific knowledge, especially with respect to exposure limits and lack of attention to risk factors for sensitive subpopulations, and
- recommended FDA to conduct an even deeper review of the scientific literature on this topic.

(3) July-Aug 2009 – Final Rule and Addendum to the 2006 White Paper [5]
- provided additional literature review and responses [6] to 2006 panel's comments and recommendations regarding 2006's draft White Paper. Essentially, there was insufficient evidence to support an association between exposure to Hg from dental amalgams and adverse health effects in humans, including sensitive subpopulations.
- issued a final Rule (21 CFR Part 872) [7] with a special control guidance document for dental amalgam and classified all components of dental amalgam (amalgam, Hg, and amalgam alloy) into Class II devices (21 CFR 872.3070) [8].
- The special controls recommended manufacturers, among other things, to add a specific labeling, including an "information for use" statement in the labeling and a performance test to determine the amount of Hg vapor released by a dental amalgam device during corrosion (ng/cm2 in 4 hrs).
- established a public-accessible website to provide dental amalgam related information
- (http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DentalProducts/DentalAmalgam/default.htm).

Since the issuance of the final rule in 2009, however, FDA had received petitions requesting a reconsideration of the rule.[aa] The petitioners raised myriad concerns, both scientific and administrative. Based on the concerns raised, the petitions requested that FDA either ban amalgam or place restrictions

[aa] Note at the time this literature review was conducted (2012), the citizen petitions had not been addressed. See Background section for information on how the citizen petitions were addressed.

on its use, especially for pregnant women, children under six, and sensitive individuals. To respond to the petitioner concerns, FDA held an Advisory Panel meeting on December 14-15, 2010.

(4) December 14-15, 2010 -- An advisory committee meeting on the human health risks of Hg vapor exposure from dental amalgam

- At this panel meeting a new risk assessment recommended by the expert consultation and the panel [9] and prepared by SNC-Lavalin, Inc., was presented. This assessment, for the first time, characterized Hg exposure from dental amalgam in the U.S. population by the number of filled amalgam surfaces and age group. Summarizing the results of this assessment, dental amalgam was the primary source of exposure to elemental Hg (Hg) in the general, non-occupationally exposed population, of which the fetus and young infant were considered to be vulnerable. Conservative estimates showed that >30% of children and >60% of adults with amalgam fillings in the U.S. were exposed to Hg from dental amalgam exceeding published RELs (EPA's RfC) for Hg vapor.
- Panel recommendations: The potential risks of Hg vapor exposure from dental amalgam need to be communicated to the public. Informed patient consent to treatment is important. FDA should consider warnings against use in sensitive groups, including pregnant women, young children, and those with kidney dysfunction or allergy to Hg.

To address the concerns of the petitioners and the advisory panel, an epidemiology review of the published literature was conducted. The sensitive groups of interest are: (1) pregnant women and their developing fetuses, (2) children under six years of age; and (3) women who are breastfeeding and nursing infants. The objective of this review is to provide a systematic literature review on the risks associated with Hg exposure from dental amalgam fillings in each of the three sensitive subpopulations.

Methods:

The primary strategy involved the search of published literature in four electronic databases (PubMed, Embase, Toxline, and DART), and employed the following search strings that were slightly modified from 2006's White Paper [5]. Specifically, changes consisted of adding more terms for health outcomes (e.g. a list of adverse effects for fetuses, newborns, pregnant women and nursing mother), more databases (i.e. added non-indexed Medline, Embase, Toxline and DART databases), and deleted the limits of "Clinical Trials" and publication date ("from 2003 to 2006").

Pubmed database

The following are three groups of terms we used on July 2, 2012.
Search #1:
("Dental Amalgam"[MeSH] OR "(amalgam OR amalgam*) AND (dental OR dentist OR dentistry OR dentist* OR filling OR fillings)" OR "mercury AND (dental OR dentist OR dentistry OR dentist*)" OR "elemental mercury" OR "mercury vapor" OR "mercury vapors" OR "mercury vapour" OR "mercury vapours" OR "Hg vapour" OR "hg vapor" OR "hg vapors" OR "metallic mercury" OR "liquid mercury")

Search #2:
#1 AND:
("adverse effects"[Subheading] OR "Risk"[MeSH] OR "toxicity"[Subheading] OR "Mercury Poisoning"[MeSH] OR "poisoning"[Subheading])

Search #3:
#2 AND
(prenatal OR “prenatal outcomes” OR “low birth weight” OR “preterm birth” OR “birth defect” OR “birth defects” OR abnormality OR abnormalities OR pregnancy OR pregnant OR fetus OR fetal OR infant OR nursing OR exposure OR maternal OR "breast milk" OR placenta OR placental OR "cord blood" OR child OR children OR baby OR newborn OR neonatal OR neonate OR preschool OR infancy OR toddler OR “pregnancy outcome” OR “pregnancy outcomes” OR neurodevelopment OR neurodevelop* OR neurotoxicity OR neurotoxic*)

Then, limit Species to “Humans”, publications to be “English” with “Abstract”.

This yielded 611 articles. Since our search strategy included MeSH Headings, it does not retrieve the records in Pubmed that have not yet been indexed (in-process records). Thus, we searched not-indexed articles using the following queries and obtained 30 additional articles:

Search	Add to Builder	Query	No. Items Found
#13	Add	Search #6 NOT medline [sb]	30
#6	Add	Search #4 AND #5	1206
#5	Add	Search (prenatal OR prenatal outcome OR prenatal outcomes OR low birth weight OR preterm birth OR birth defect OR birth defects OR pregnancy OR pregnant OR fetus OR fetal OR fetuses OR infant OR nursing OR maternal OR breast milk OR placenta OR placental OR cord blood OR children OR child OR baby OR babies OR toddler OR newborn OR neonatal OR neonate OR preschool OR infancy OR neurodevelopment OR neurodevelopmental OR neurotoxicity OR pregnancy outcome OR pregnancy outcomes OR abnormalities)	3836597
#4	Add	Search #1 OR #2 OR #3	11530
#3	Add	Search mercury AND (dental OR dentist OR dentistry OR dentist*)	2944
#2	Add	Search (amalgam OR amalgam*) AND (dental OR dentist OR dentistry OR dentist* OR filling OR fillings)	9230
#1	Add	Search “elemental mercury OR “mercury vapor” OR “mercury vapors” OR “mercury vapours” OR “hg vapour” OR “HG vapor” OR “hg vapors” OR “metallic mercury” OR “liquid mercury”	1818

Similar search terms were used to search databases of Embase, Toxline, and DART. Terms used, and search results are presented as Appendix 1.

Eligibility criteria: Searches were limited to articles published in English with Hg exposure stemming from dental amalgam and no limit on publication dates.

Study Selection: The review team decided to include articles for full text review only if they met the following criteria:

1. articles that evaluated the correlations and/or health effects(risks) of dental amalgam in one of the three sensitive groups;
2. all original research articles
3. case series with greater than nine subjects;
4. literature reviews, in which the review process was conducted in a systematic manner with clear definition of terms/key words used to search databases and a clear screening process was described.

When an individual reviewer was not certain whether to exclude an article, the final decision was adjudicated by the entire team of reviewers.

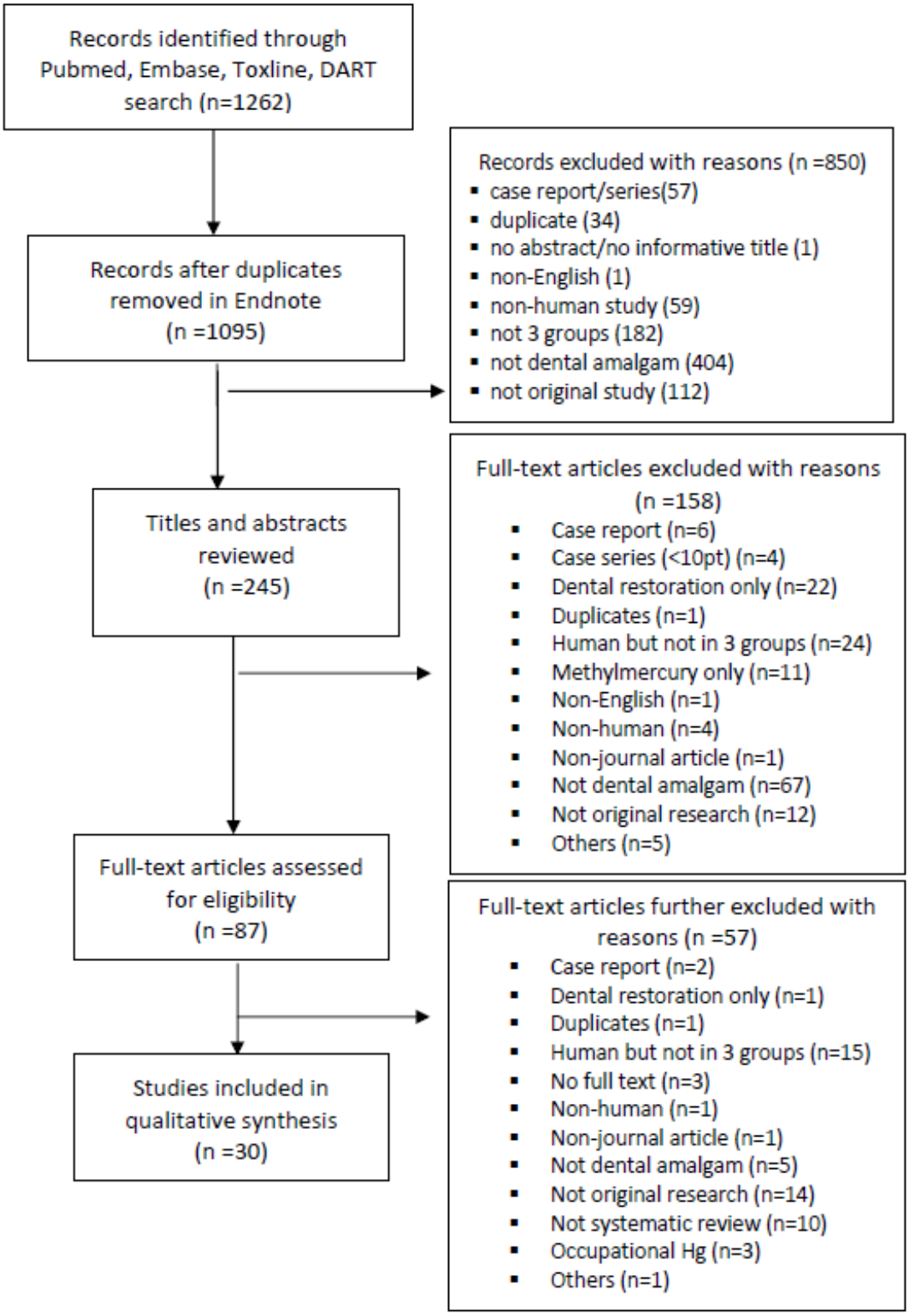
Data collection process: The abstracts were first reviewed and screened to identify articles that will go through full text review. Then, the full text review articles were split amongst four reviewers who assessed the eligibility for inclusion/exclusion (Figure 1) and the study results. The review team decided on the eligibility of all articles that were included in the final assessment. The study results from the final articles were extracted and tabulated into two tables (Tables 1-2).

Data items: Due to the specific interests of the subpopulations of this literature review, the following data variables were summarized into detailed results (Table 2): first author's last name, study design, study population (list age when possible), sample size, study endpoints, Hg source (e.g. dental amalgam, food consumption), Hg sample measured(e.g. urine, hair, blood), results/conclusion.

The following abbreviations are used throughout this document:

Hg: mercury
[Hg]: mercury concentration
T-Hg: total mercury (inorganic plus organic Hg compounds) [11, 12]
I-Hg: inorganic mercury [11]
MeHg: methymercury [11]

Figure 1 Flow Diagram of article retrieval and selection



Summary of Results

Overview of Studies

A full diagram of article retrieval and selection appears in Figure 1. In summary, the above search yielded 611 articles from PubMed and 30 non-indexed Medline, 355 articles from Embase, 209 articles from Toxline, and 57 articles from DART. The raw total was 1262 articles, of which 1095 remained after removing duplicates in Endnote. The 1095 articles were initially screened to exclude non-human studies and studies not pertaining to dental amalgam studies in any of the three sensitive groups. The remaining 245 articles were further screened. A total of 158 articles were excluded during the initial screening for the following reasons: case report (n=6), case series (with<10 subjects) (n=4), dental restoration only (n=22), duplicates (n=1), human studies but none specified 3 groups (n=24), methylmercury only (n=11), non-English (n=1), non-human (n=4), non-journal article (n=1), not dental amalgam (n=67), not original research (n=12), and others (n=5).

The full-texts of the remaining 87 articles were examined by reviewers for eligibility, of which 57 were excluded for the following reasons: case report (n=2), dental restoration only (n=1), duplicates (n=1), human studies but none specified 3 groups (n=15), no full text available at time of this review (n=3), non-human (n=1), non-journal article (n=1), not dental amalgam (n=5), not original research (n=14), not systematic review (n=10), occupational Hg (n=3), and other (n=1). Thus, thirty full-text articles remained for detailed assessment in this review. A summary of the design of these thirty studies is listed below (Table 1), and more detailed results are listed in Table 2 at the end of the review.

Table 1 Study design of all publications included within this report (N=30). 'Study Population' was numbered in accordance with sections below, 1-Pregnant Women and Their Developing Fetuses; 2-Children under six years of age; 3- Women who are breastfeeding and nursing infants.

First Author	Year	Study Design	Study Location	Study Population (group numbered)	Sample Size
Al-Saleh	2011	Cross-sectional	Saudi Arabia	2	182 children
Al-Saleh	2012	Cross-sectional	Saudi Arabia	2	182 children
Altmann	1998	Cross-sectional	Germany	2	384 children
Barghi	2012	Case series	Iran	1	100 preg. women
Cordier	1998	Cross-sectional	France	1, 2	109 pregnant women, 136 children
Da Costa	2005	Cross-sectional	Brazil	3	23 mothers
Daniels	2007	Prospective cohort	U.K.	1, 2	7,375 preg. women, mothers, and newborns
Drasch	1994	Retrospective cohort	Germany	1,2	108 autopsies

First Author	Year	Study Design	Study Location	Study Population (group numbered)	Sample Size
Drasch	1998	Case series	Germany	3	46 mothers, 9 formula
Drexler	1998	Case series	Germany	3	85 mothers
El-baz	2010	Case-control	Egypt	2	32:15 autistic vs non-autistic children
Geer	2012	Case series	US	1	189 preg. Women, 78 cord blood samples
Geier	2009	Case-control	US	2	100 mother-child pairs
Gundacker	2002	Cross-sectional	Austria	3	165 mothers
Hertz-Picciotto	2010	Case-control	US	2	309:143 autistic vs. non-autistic children
Hujoel	2005	case-control	US	1, 2	5179 singleton births and 197 multiple births
Khordi-Mood	2001	Prospective cohort	Iran	2	43 children
Levy	2004	Case-control	Canada	2	60 children, 34:26 cases vs control with amalgam fillings
Lindow	2003	Cross-sectional	UK	1	53 preg. women-infant pairs. Groups(24:29:9) without, with amalgams but not during pregnancy, and with amalgam during pregnancy
Luglie	2005	Prospective cohort	Italy	1	72 pregnant women, 53:19 with and without amalgams
Lutz	1996	Case series	Sweden	1, 2	20 fetuses and 15 infants
Orun	2012	Cross-sectional	Turkey	3	144 mothers
Oskarsson	1996	Cross-sectional	Sweden	3	30 mothers

First Author	Year	Study Design	Study Location	Study Population (group numbered)	Sample Size
Palkovicova	2008	Survey	Sovakia	1	99 mother-child pairs
Risher	2003	Systematic review	NA	NA	NA
Unuvar	2007	Prospective cohort	Turkey	1	143 mother-newborn pairs
Ursinyova	2005	Cross-sectional	Slovakia	3	158 mothers
Ursinyova	2012	Cross-sectional	Slovak	1,2	75 pregnant woman and child pairs
Vahter	2000	Longitudinal	Sweden	1, 3	254 preg. women
Watson	2011	Prospective cohort	US	1,2	587 mother-child pairs

Abbreviations: UK: United Kingdom, US: United States, preg.: pregnant, NA: not available.

1. Pregnant Women and Their Developing Fetuses

There were 14 articles that studied Hg exposures in pregnant women and their developing fetuses. Among them, there were 11 observational studies and three case series (Table 1).

Maternal exposure and fetal exposure

The human Hg exposures were estimated with differing approaches (number of dental amalgams fillings, I-Hg, and Hg,) and in differing biospecimen types:

- Twelve of these studies evaluated Hg levels in the following, with some studies evaluating more than one bio-specimen:
  - pregnant women's hair, blood or urine [11, 13-20],
  - cord blood [11, 15, 16, 18, 20],
  - amniotic fluid [21],
  - fetal tissues [22, 23], and
  - infant hair [17].

- Eleven studies measured the correlation between maternal I-Hg concentrations and [Hg] in:
  - maternal or infant hair [13, 14, 17],
  - maternal blood and cord blood [11, 18-20],
  - maternal blood and meconium [19],
  - maternal urine and cord blood [16],
  - maternal hair and cord blood [17], and
  - T4 levels in pregnant women [11].

- Seven studies evaluated the correlation between the number of dental amalgams fillings and Hg levels in:
    - maternal blood [13, 14]
    - amniotic fluid [21],
    - cord blood [18],
    - fetal tissues [22, 23], and
    - maternal urine [16].

In studies that evaluated I-Hg in blood or urine, three studies presented measures in µg/g [13, 19, 20], three in mg/g [14, 15], one presented in ng/g [22], four presented in µg/L [11, 16-18], and two [21, 23] presented findings in µg/L per kg wet weight. For purposes of comparison, findings were converted to µg/g, where possible.

Among the 11 studies that evaluated differences in Hg levels in various fetal or infant tissues or cord blood and number of amalgams in the pregnant woman [11, 13, 14, 16-23], all found significant correlations between the number of amalgams and I-Hg or T-Hg (when accounting for MeHg). Six of these 11 studies also evaluated the correlation between maternal Hg levels and fetal/newborn Hg levels. Five of the six studies found significant correlations between measures [11, 18-20, 23] (Table 2). The levels of I-Hg in pregnant women varied from 0.19 to 0.56 µg/g for readings to geometric means from 1.03 to 3.1 µg/g in hair and with similar levels in maternal urine or blood. Cord blood levels were slightly higher, ranging from 0.50 µg/g to a geometric mean of 2.14 µg/g. Infant hair Hg ranged from 0.17 to 0.44 µg/g.

Some studies looked solely at the relationship between cross-sectional measures, while others evaluated the timing of dental amalgam placements and Hg levels changes over the course of pregnancy [11, 13, 17, 18, 24]. The Hg level is negatively correlated with the number of days after delivery ($r = -0.26$, $p=0.04$) with the level of Hg highest at delivery, decreasing until day 5, then stabilizing afterwards [24]. Palkovicova [18] and Barghi [13] reported a significant linear relationship between the number of years since the latest amalgam fillings and the level of Hg in cord blood ($R=0.22$, $P=0.0462$) [18] or if the last amalgam filling was less than 30 months before the pregnancy [13]. Lindow [17] also found that the maternal and fetal hair Hg levels were significantly higher in women who previously had dental amalgam placed. However, there was no appreciable increase in maternal and fetal hair Hg levels when new dental amalgams were placed during pregnancy.

<u>Maternal exposure and outcomes in pregnancy or infant development</u>

Three out of the 14 studies evaluated the relationship between the number of dental amalgams in pregnant women and/or I-Hg or T-Hg levels and health outcomes in pregnancy or infant development [19, 21, 25]. The health outcomes studied were birth weight [25], newborn and pregnancy outcomes [19, 21]. Two studies did not find any effect on birth outcome or pregnancy even though the number of fillings increased Hg in venous blood and cord blood significantly [19] and [Hg] in amniotic fluid [21].

Hujoel [21] also reported that non-significant associations between dental amalgams and birth weight from a population-based case-control study (cases are women with low birth weight, control are those with normal birth weight). Notably, women with at least one Hg-containing amalgam filling during pregnancy (n=249) were not at an increased risk for a low-birth-weight infant (OR=0.75, 95% CI: 0.45, 1.26), and neither were women who had 4–11 amalgam fillings placed (OR=1.00, 95% CI: 0.27, 3.68). They also described a "weak dose-response" when analyses were limited to women with normal birth weight infants, i.e. birth weight decreased by 9 grams (95% CI: 32-15, p=0.48) as the number of amalgams increased.

Thyroid hormones are involved in many metabolic processes and child development, and therefore have been studied as biomarkers to infer health outcomes. Ursinoyova [20] reported the median T-Hg and MeHg levels in maternal blood and cord blood were 0.50, 0.53 and 0.22, 0.32 µg/L, respectively. There were significant correlations between paired maternal–cord blood levels for T-Hg and MeHg, with a greater transplacental transport of MeHg compared with T-Hg (mean cord/maternal blood ratio, 1.80 vs. 1.24), which affect thyroid hormone status during prenatal and early postnatal. There was a significant negative association between T-Hg and free thyroid fT4 ($r=-0.231$, $p<0.05$) in pregnant women. This association was not statistically significant ($p>0.05$) for methymercury (MeHg) blood levels, thus I-Hg (subtraction of MeHg from T-Hg) likely contributed to the significant association between T-Hg and fT4.

2. Children under six years of age

There were 14 articles that evaluated the effects/risks associated with Hg exposure from dental amalgam fillings for children under six years old. Among them, there were 13 observational studies and one case series (Table 1).

Among the articles reviewed, Hg levels were measured in different bio-specimens, such as (1) urine [26-30], (2) blood [15, 20, 31], (3) hair [14, 26, 32], (4) kidney/renal cortex and brain/cerebral cortex [22, 23], (5) liver [22], and (6) toe-nails [26]. Two studies did not measure any Hg levels [33, 34]. Most of the studies presented Hg measures in micrograms/gram (µg/g), four studies presented in micrograms/liter [20, 26, 29, 31] and only one study measured Hg parts per million (PPM) [32]. The Hg exposure levels ranged from 0.16 to 2.746 µg/g in urine, 0.44 to 0.66 µg/g in blood, 0.717 to 2.5 µg/g in hair (see Table 2). The follow-up period ranged from 30 days to 66 months.

Eight of the 14 studies found the [Hg] in the children's bio-specimens were significantly correlated ($p < 0.05$) with the number of dental amalgam fillings or the amalgam surface areas of the mother [14, 20, 22, 23, 26, 29, 30] and children themselves [29]. These bio-specimens were taken from children in various age groups, ranging from 1 day to 8-years old (Table 2). The rest of the studies did not find such correlations, and some discussed some possible reasons such as small sample size and the presence of factors confounding the association.

Nine articles studied the effects/risks of maternal dental amalgams and Hg levels on children's health outcomes. Five of the studies investigated the association with neurodevelopmental disorders [15, 31-34]. Particularly four [15, 31-33] studied autism. Of the four studies, only one found a significant association with autism [33]. Although there was no significant difference in prenatal number of amalgams, Geier [33] found that the odds of severe autism vs mild autism was significantly increased in mothers with 8 or more amalgams (OR=4.4, p=0.03), and subjects with ≥6 amalgams were 3.2-fold more likely to be diagnosed with severe autism, in comparison to mild autism, than subjects with ≤5 amalgams ($p<0.05$).

For neurodevelopmental outcomes, one study [34] reported a sub-group analysis and found an association between amalgam restoration during gestation and scholastic achievement in boys in two of the six frequently used tests of scholastic achievement. However, prenatal dental amalgams (mean: 5.1 surfaces) were not associated with six neurodevelopmental outcomes. In contrast, a study by Daniels et al. [15] did not find any association (OR = 0.9, 95% CI: 0.6, 1.4) between dental care, including amalgam fillings, before and during pregnancy in relation to birth outcomes and cognitive development in children up to 15 months old.

In addition to neurodevelopmental outcomes, the maternal dental amalgam exposure and maternal Hg levels were examined in relation to other health outcomes and health-related biomarkers, i.e. birth weight (n=1), oral health (n=1), renal function (n=1), visual outcomes (n=1) and thyroid hormone levels (n=1) (Table 2). These assessments were not performed at a standard age but at various ages through six years. In particular, associations between maternal dental fillings were reported for aphthous ulcers, white patches and burning mouth sensation [26] and increased urine creatinine as a biomarker for abnormal kidney tubular functions [27]. Maternal Hg levels in urine and blood were associated with visual outcomes [28] and thyroid-stimulating hormone [20], respectively.

3. Women who are breastfeeding and nursing infants

Seven studies [24, 35-40] were identified in our literature review as studies on the effects of dental amalgam in lactating and nursing women. Among them, there were five cross-sectional studies and two case series (Table 1). All reported correlations between the amalgam exposure [35], number of fillings [24, 37-40] or both [36] with concentrations of Hg in breast milk. Some studies [35, 39] used the mean [Hg] in breast milk to assess the risk of Hg intake by breast-fed babies. The authors extrapolated the risk of Hg intake based on expected weight of the nursed infants and used assumptions for expected breast milk intake.

Mercury was measured in the breast milk within the range of one (day of birth) to sixty days postpartum. The range of mean Hg levels in breast milk was 0.6 to 5.73 ng/g. One study [35] reported a significant correlation between number of maternal amalgam surfaces and total Hg in breast milk. In addition, in this population where the authors defined as women with low consumption of fish (self-

reported average intake of fish is one meal per week), the author extrapolated from average milk consumption that 56.6% of breastfed infants were exposed to mercury concentrations higher than the recommended World Health Organization reference value for inorganic mercury (0.5 ug/kg/body weight). Four [36, 38-40] did not observe a statistically significant correlation between dental amalgam and mean Hg levels in breast milk.

Critique and Assessment

The currently available 14 peer-reviewed articles on Hg exposure among pregnant women, their developing fetuses and newborns, consistently showed significant correlation between the maternal dental amalgams and/or Hg levels to fetal Hg levels in various tissues. However, there were only three studies that investigated the direct health outcomes for pregnant women and their developing fetuses and newborns, and no significant association was found. Only one out of one biomarker study found a significant correlation between paired maternal–cord blood levels for T-Hg and MeHg, with a greater transplacental transport of MeHg compared with T-Hg.

For children under six years old, there were inconsistent results between children's Hg levels and their maternal Hg levels and/or dental amalgam fillings. Specifically, a little over half of the fourteen studies found the [Hg] in the children's bio-specimen were correlated significantly ($p < 0.05$) with the number of dental amalgam fillings or the amalgam surface areas of the mother [14, 17, 20, 22, 23, 26, 29, 30]. Additionally, no consistent trend in children's health outcomes was reported among nine studies. Four out of five studies on neurodevelopment did not find any significant associations. The only one that reported significant associations (OR=4.4, p=0.03) with autism [33] was only found between severe autism versus mild autism among mothers with eight or more amalgams. Another four studies reported associations with other health outcomes (e.g. birth weight, oral, visual, renal and thyroid-stimulating hormone) [15, 20, 26, 28].

Studies on the effects of dental amalgam in lactating and nursing women only reported correlation between dental amalgam and mean [Hg] in breast milk levels. None of the seven articles examined Hg exposure from dental amalgam in nursing/lactating mothers on health outcomes with regards to either the nursed infants or mothers. The correlation between dental amalgam and Hg levels in breast milk levels were inconsistent because four did not observe a statistically significant correlation while the other three did.

There are some common issues across all studies. First of all, the correlations between maternal dental amalgams or Hg levels in pregnant women and Hg levels in children (28 days-6 years old) and in breast milk are inconsistent. The inconsistency could be due to various data collection methods and data analysis methods. For example, some studies did not separate different sources of Hg intake to the pregnant women and nursing mothers, e.g. from food (particularly fish) consumptions, environmental Hg contamination, cosmetic uses [23, 32]. Some did not separate different types of Hg (e.g. T-Hg, MeHg,

I-Hg) or measured in multiple specimens (e.g. urine, blood, hair, nails). The sample sizes varied greatly among the 30 articles, ranging from 35 samples (20 fetuses and 15 infants [23]) to over 5000 subjects [15, 25]. The study populations differed even within the same group. For example, publications on children have a wide range of ages, from one day to five years old in one study [22] and five to fifteen years old in other studies [26, 27]. Of all fourteen studies in children, only about half of them adjusted for confounders, e.g. gender, age, BMI, resident locations, food, hair products, and dental amalgam categories.

Data analysis methods also could have affected the results. For example, studies showed positive correlations only when amalgam fillings were categorized (e.g. 1-4 fillings, 5-7 fillings, >=8 fillings) rather than when using the continuous measures (e.g. amalgam surface areas, number of fillings). Subgroup analysis has revealed some trends that were not available with the whole population. Watson [34] did not find any significant association between dental amalgam fillings and six neurodevelopmental outcomes when using all children's data together. However, a significant drop in two of the six neurodevelopmental tests was found in boys, but not girls. In contrast, Cordier [14] discovered a significant difference in the Hg levels for amalgam vs. no amalgam when combining data from both mother and children. Some studies considered or stratified the possible confounding factors; however their correlations and/or associations are not consistent either [14, 19, 22, 26-28, 30, 31, 33, 34].

The associations between the increased number of amalgam fillings (or increased Hg levels) on health outcomes in children have also not been consistently reported across all studies. Besides the above factors, different disease diagnosis and classifications (e.g. autism severities) may have also contributed to the controversies. For example, Geier [33] examined increased Hg exposure from maternal dental amalgams during pregnancy and paired children diagnosed with DSM-IV autism (severe) or ASD (mild), while other studies did not distinguish different levels of autism [15, 31, 32]. Socio-economic status (SES) was found to be a strong confounding factor in a study that did not find amalgams contributed to Hg levels or early cognitive development [15]. Notably, no articles have studied the risks of direct amalgam fillings in children under six.

Additionally, all the studies assumed a linear relationship, and none explored non-linear relationships. Some studies referred to the WHO standards as the guidance to infer the acceptability of the mean Hg levels. None distinguished the percentages of contributions of dental amalgam to the T-Hg burden in bio-specimen. The limited evidence based on dental amalgam precludes any conclusions on the risks of dental amalgam fillings on health outcomes of pregnant women and developing fetuses, children under six, and lactating and nursing women.

Conclusions

Based on the current available literature (30 articles in total), our findings are consistent with previous literature reviews [3-5, 9] conducted by several agencies.

For pregnant women and their developing fetuses or newborns, one consistent finding is that all eleven studies reported significant correlations between maternal dental amalgams and fetal/newborn's Hg levels. However, only three studies [19, 21, 25], with study design limitations (Table 1), examined health outcomes for these populations. Each of the three reported no associations with any health outcomes.

The maternal dental amalgams did not show consistent correlations with the Hg levels in breast milk, nursed infants, or young children (newborn to six years old). Moreover, in terms of health outcomes, the results are more sporadic and inconsistent. No consistent results showed that the prenatal or maternal dental amalgams would increase the risks of children's Hg levels or their health outcomes, although gender differences were detected in a couple studies. The Hg levels of pregnant women decrease over pregnancy possibly through the movement of Hg from the mother to the fetuses/newborns.

The literature reviewed provides evidence in support of an association between dental amalgams in pregnant women and the Hg levels in the women and their developing fetuses or newborns. The literature, while not providing conclusive evidence of adverse health effects, raises concern with respect to potential adverse effects within these two populations. However, with limited information from the literature, no conclusions can be made for children under six years of age and women who are breastfeeding and nursing infants.

1 **Table 2 Key data extracted from references cited in this document**

First Author	Study Design	Study Population	Sample size	Study Endpoints	Hg source	Hg sample measured	Result/Conclusion
Al-Saleh, 2011 [26]	Cross-sectional	Saudi Arabia, children <6yr (5-15 yr)	182 children	[Hg] in urine, hair and toe nails, and creatinine in urine, aphthose ulcers, white patches, and a burning mouth sensation	amalgam filling	urine, hair, nail, creatinine	Amalgams are associated with mercury in urine, hair and nails, and associated significantly with aphthous ulcers, white patches and burning mouth sensation.
Al-Saleh, 2012 [27]	Cross-sectional	Saudi Arabia, children <6yr (5-15 yr)	182 children	UHg-C, oxidative stress biomarkers (MDA and 8-)HdG)	amalgam filling	urine	Amalgams are associated with mercury excreted in urine, an effect on kidney tubular functions.
Altmann, 1998 [28]	Cross-sectional	Germany, children <6yr (5.0-7.8 yr)	384 children	UHg, Visual-Evoked potentials (VEPs) and Contrast Sensitivity (CS)	amalgam filling	urine	Subtle changes in visual-evoked potentials and contrast sensitivity was found with even at very low urine Hg.
Barghi, 2012 [13]	Case series	Iran, pregnant woman	100 preg. women	Hg levels in hair. No health outcomes.	amalgam filling	hair	There was a significantly higher mercury for 4-7 fillings and if last filling was less than 30 months and was highest if both of those were present together
Cordier, 1998 [14]	Cross-sectional	French, pregnant woman, children <6yr	109 pregnant women, 136 children	dental amalgam#. No health outcomes.	others	hair	Amalgams did not contribute to mercury levels, however, significant difference for amalgam vs. no amalgam adults and children combined.
Da Costa, 2005 [35]	Cross-sectional	Brazil, nursing mothers	23 mothers	[Hg] in breast milk. No health outcomes.	amalgam filling	breast milk	No health outcomes. Correlation study between amalgam surfaces & [Hg] in breast milk in first month postnateal.

First Author	Study Design	Study Population	Sample size	Study Endpoints	Hg source	Hg sample measured	Result/Conclusion
Daniels, 2007 [15]	Prospecti ve cohort	UK, pregnant woman, fetus, children <6yr (15 months)	7,375 preg. women, mothers, and newborn s	mother's amalgam# (0, 1, 2-3, 4+) before or during pregnancy, T-Hg in umbilical cord, child birth outcomes and early cognitive development	amalgam filling	blood	Amalgams did not contribute to mercury levels or early cognitive development, however there was a strong socio-economic status confounding factor.
Drasch, 1994 [22]	Retrospe ctive cohort	Germany, children <6yr (1d-5 yr.), fetus	108 autopsie s	mother's amalgam# (0 - 2, and >10). [Hg] in liver, renal (cortex) and cerebral (cortex).	amalgam filling	liver, renal (cortex), and cerebral (cortex)	Number of amalgams in the mother was correlated with [Hg] in children's liver and renal tissues.
Drasch, 1998 [24]	Case series	Germany, nursing mothers	46 mothers in day 2-7 post-partum compare d to 9 milk formula samples	[Hg] in breast milk. No health outcomes.	amalgam filling	breast milk	[Hg] in breast milk increase with number of amalgams. Level of Hg is highest at delivery and decreases to day five, then stabilizes.
Drexler, 1998 [36]	Case series	Germany, nursing mothers	85 mothers	[Hg] in breast milk. No health outcomes.	amalgam filling	multiple	The [Hg] in breast milk and urine correlated with amalgam surfaces/filings at (a) 1st week of birth, but lost after 2 months of lactation. amalgam but with fish consumption.
El-baz, 2010 [32]	Case-control	Egypt, children <6yr	32:15 autistic vs non-autistic children	History of maternal dental amalgams, and HHg in children. No health outcomes.	amalgam filling	hair	Amalgams are related to autism but not statistically significant. However, the levels of mercury from all sources combined were significantly correlated with autism.

First Author	Study Design	Study Population	Sample size	Study Endpoints	Hg source	Hg sample measured	Result/Conclusion
Geer, 2012 [16]	Case series	US, pregnant woman, fetus	189 preg. Women, 78 cord blood samples	[Hg] in urine and cord blood. No health outcomes.		urine, blood	In the full dataset of 175 women, dental amalgams and foreign birth was positively associated with urine mercury, it was not significant in the 72 cord blood samples
Geier, 2009 [33]	Case-control	US, children <6yr	100 mother/child pairs	maternal amalgam# and autism in children	amalgam filling	NA	There was no significant difference in prenatal number of amalgams. However, the odds of severe vs. mild autism was significantly increased for >=8 amalgams.
Gundacker, 2002 [37]	Cross-sectional	Austria, nursing mothers	165 mothers	[Hg] in breast milk. No health outcomes.	amalgam filling	breast milk	No health outcomes. Correlation study between #filings & [Hg] in breast milk. 8% breast milk samples has [Hg]> 3.5ug/L.
Hertz-Picciotto, 2010 [31]	Case-control	US, children <6yr (2-5 yr)	309:143 autistic vs. non-autistic children	Amalgam#, Hg in blood, and autism vs non-autism	amalgam filling	blood	Amalgams are not related to autism even after adjusted other factors.
Hujoel, 2005 [25]	case-control	US, pregnant woman, newborn	5179 singleton births and 197 multiple births	maternal amalgam# and birth weight	amalgam filling	NA	Amalgam fillings during pregnancy was not statistically associated with low birth weight as a number of as a dose-response, nor was there an association with birth weight in new born infants
Khordi-Mood, 2001 [29]	Prospective cohort	Iran, children <6yr (5-7 yr)	43 children	children's amalgam# and amalgam surfaces, UHg.	amalgam filling	urine	There was a statistically significant correlation between amalgam fillings and urinary Hg. However, no statistically significant dose-response relationship.
Levy, 2004 [30]	Case-control	Canada, children <6yr (4-8 yr)	60 children. 34:26 cases:control	History of amalgams. Urine Hg excretion	amalgam filling	urine	Amalgam fillings leads to an increased odds of high urinary Hg.

First Author	Study Design	Study Population	Sample size	Study Endpoints	Hg source	Hg sample measured	Result/Conclusion
			with and without amalgam fillings				
Lindow, 2003 [17]	Cross-sectional	UK, pregnant woman, fetus	53 mother/infant pairs. Group 1 (no amalgams)=24, Group 2 (had amalgams, but not during pregnancy) n=29, Group 3 (amalgam during pregnancy) n=9	[Hg] compared to amalgam# and if placed during pregnancy	amalgam filling	hair	Maternal and fetal hair mercury levels were significantly higher in women who previously had dental amalgam placed. However, placement during pregnancy did not show increase of maternal or fetal hair mercury level.
Luglie, 2005 [21]	Prospective cohort	Italy, pregnant woman	72 pregnant women, 53:19 with and without amalgams	[Hg] in amnoitic fluid, amalgam filling# and surface, obstetric history and perinatal complications	amalgam filling	amnoitic fluid	[Hg] in amniotic fluid is higher (not significant) in patients with higher number and surface of fillings; not significantly affect pregnancy or newborns.

First Author	Study Design	Study Population	Sample size	Study Endpoints	Hg source	Hg sample measured	Result/Conclusion
Lutz, 1996 [23]	Case series	Sweden, fetus, children <6yr (28d-3 months)	20 fetuses and 15 infants	Level of Hg in brain and kidney samples		brain, kidney	There was a significant correlation between amalgam filling# and fetal or infants' renal [Hg] when evaluated categorically.
Orun, 2012 [38]	Cross-sectional	Turkey, nursing mothers	144 mothers	[Hg] in breast milk. No health outcomes.	amalgam filling	breast milk	No health outcomes. No statistical difference between women with no filling and women with at least one filling. But no adjustment by fish consumption and viscera.
Oskarsson , 1996 [39]	Cross-sectional	Sweden, nursing mothers	30 mothers	[inorganic Hg] in blood & breast milk. No health outcomes.	amalgam filling	blood, breast milk	No health outcomes. Correlation study between amalgam surfaces/filings & inorganic Hg in mother's blood & breast milk with #fillings. Exposure of infant to mercury from breast milk was calculated to range up to 0.3ug/kg.
Palkovicova, 2008 [18]	Survey	Sovakia, pregnant woman, fetus	99 mother-child pairs	Amalgam#	amalgam filling	cord blood	Multivariate linear regression models, amalgam and time to most recent dental filling remained significant. Strongest predictor of cord blood Hg levels was [Hg] in maternal blood
Risher, 2003 [12]	Systematic review	NA	NA	NA	NA	NA	Dental amalgam contributes significantly to mercury body burden, and no consistent association was found between dental amalgam and neurotoxicity.
Unuvar, 2007 [19]	Prospective cohort	Turkey, pregnant woman, newborn (<28d)	N=143 mother-newborn pairs	Hg levels in mom, cord and meconium, birth outcomes	amalgam filling	blood	The number of fillings increased mercury in venous blood and cord blood at a statistically significant, but no effect on birth outcome seen.
Ursinyova, 2012 [20]	Cross-sectional	Slovakia, nursing mothers	158 mothers	[Hg] in breast milk. No health outcomes.	amalgam filling	breast milk	No health outcomes. Correlation study between amalgam surfaces/filings & Hg in breast milk, higher [Hg] in breast milk than in infant formula.

First Author	Study Design	Study Population	Sample size	Study Endpoints	Hg source	Hg sample measured	Result/Conclusion
Ursinyova, 2005 [40]	Cross-sectional	Slovak, pregnant woman, fetus, children <6yr (35-42 weeks)	N=75x2, pregnant woman and child pairs	maternal amalgam, thyroid hormones	amalgam filling	blood	Low-exposure to Hg (including dental amalgam) can affect thyroid hormone status during prenatal and early postnatal stages. Maternal THg is significant correlated with Hg in cord blood, and both are correlated with children's free thyroxin (fT4) and thyroid-stimulating hormone (TSH).
Vahter, 2000 [11]	Prospective cohort	Sweden, pregnant woman, fetus, nursing mother	254 preg. women	Number of amalgams, Hg changes during pregnancy	amalgam filling	blood	Significant correlation between IHg in cord blood to maternal blood, both maternal and cord blood increased IHg with number of amalgams. IHg decreased 6% during pregnancy, the decrease accelerated after delivery.
Watson, 2011 [34]	Prospective cohort	US, pregnant woman, children <6yr	N=587 mother-child pairs	prenatal amalgam, 6 neurodevelopment tests	amalgam filling	hair	prenatal dental amalgam mercury exposure had not significant association with neurodevelopment; effects differ by gender.

Abbreviations
UK: United Kingdom, US: United States, preg.: pregnant, NA: not available.
[Hg]: Hg concentration, UHg-Hg in urine, HHG--Hg in hair, NHg: in nails, Uhg-C: in urinary creatinine

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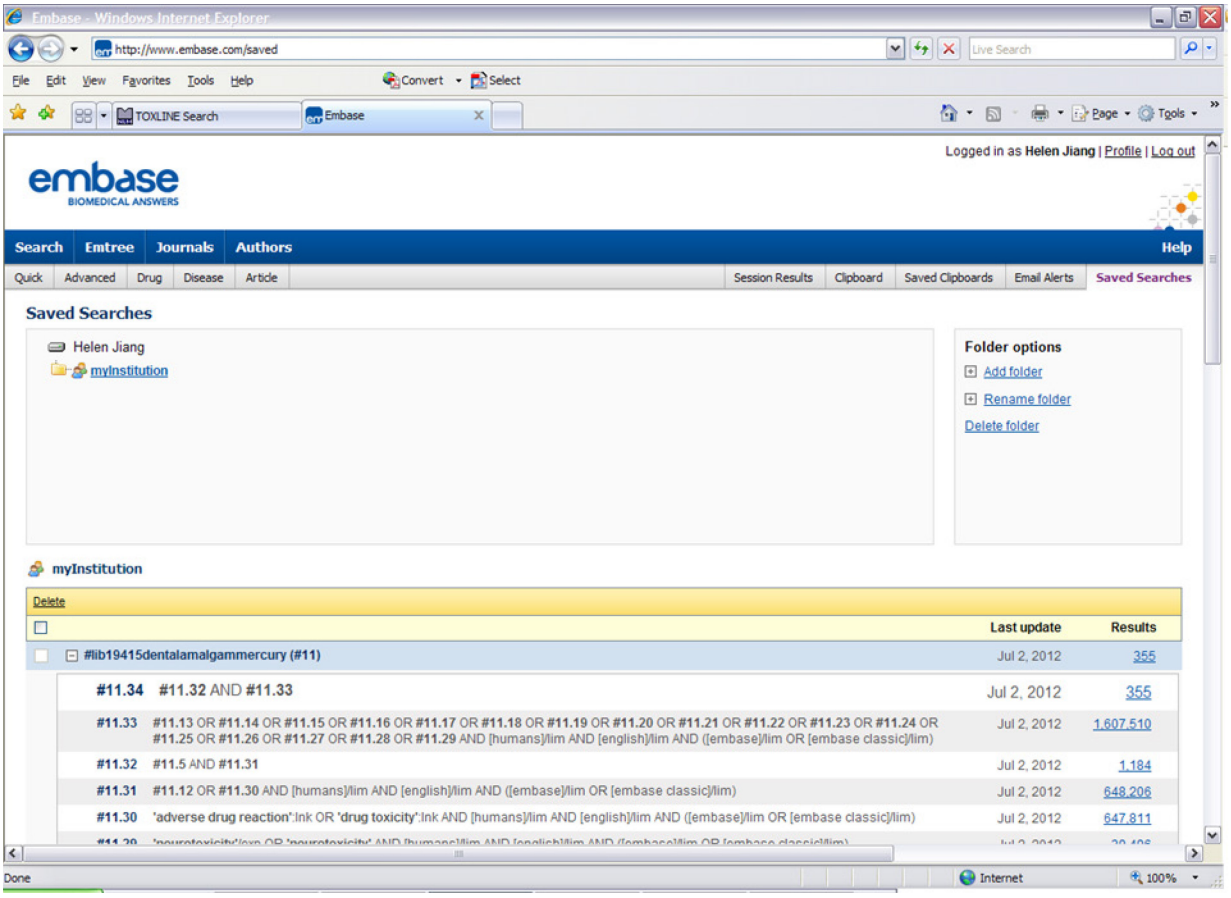
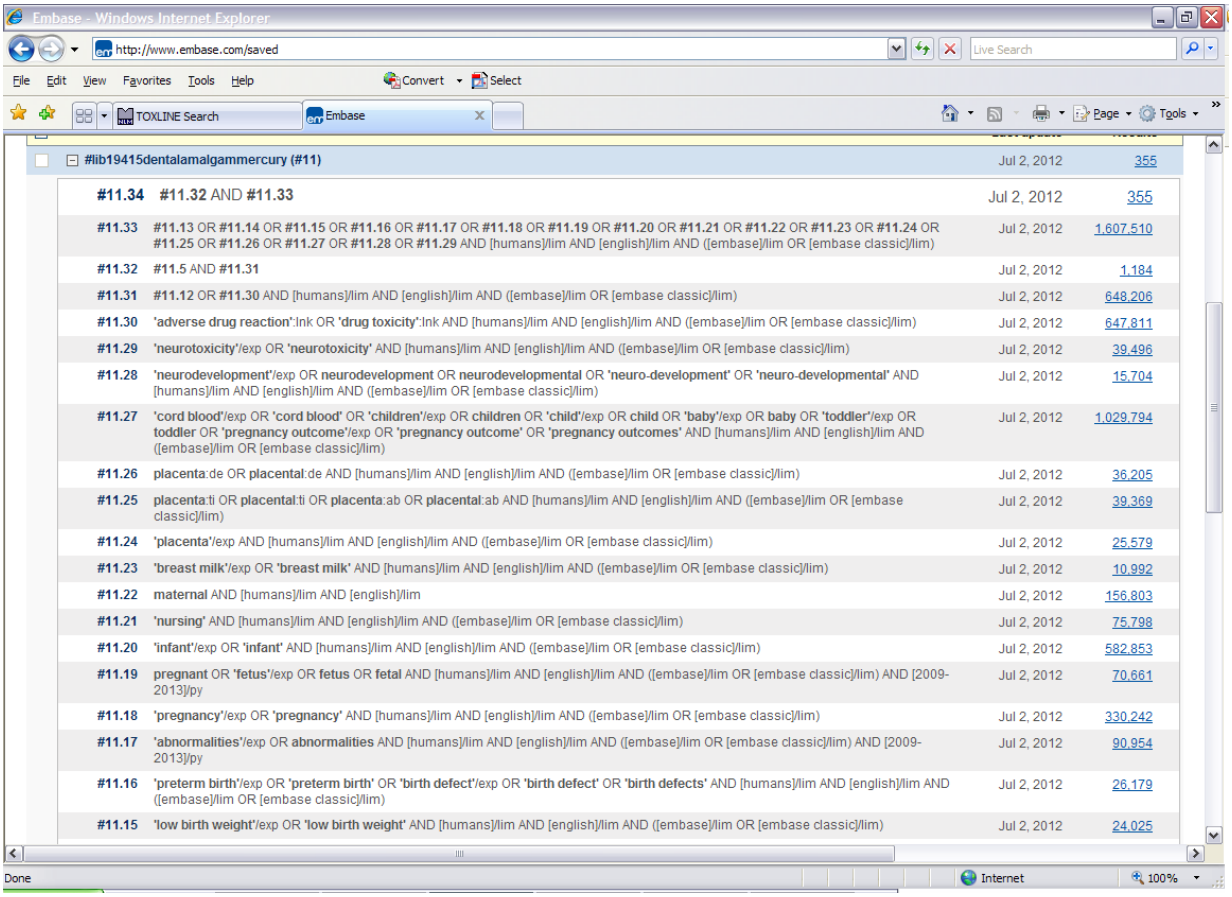
Appendix 1: Embase, Toxline, and DART search queries and results

1. Embase database [see Appendix 1]

The following are three groups of terms we used on July 2, 2012.





	#lib19415dentalamalgammercury (#11)	Jul 2, 2012	355
#11.34	#11.32 AND #11.33	Jul 2, 2012	355
#11.33	#11.13 OR #11.14 OR #11.15 OR #11.16 OR #11.17 OR #11.18 OR #11.19 OR #11.20 OR #11.21 OR #11.22 OR #11.23 OR #11.24 OR #11.25 OR #11.26 OR #11.27 OR #11.28 OR #11.29 AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim)	Jul 2, 2012	1,607,510
#11.32	#11.5 AND #11.31	Jul 2, 2012	1,184
#11.31	#11.12 OR #11.30 AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim)	Jul 2, 2012	648,206
#11.30	'adverse drug reaction':lnk OR 'drug toxicity':lnk AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim)	Jul 2, 2012	647,811
#11.29	'neurotoxicity'/exp OR 'neurotoxicity' AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim)	Jul 2, 2012	39,496
#11.28	'neurodevelopment'/exp OR neurodevelopment OR neurodevelopmental OR 'neuro-development' OR 'neuro-developmental' AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim)	Jul 2, 2012	15,704
#11.27	'cord blood'/exp OR 'cord blood' OR 'children'/exp OR children OR 'child'/exp OR child OR 'baby'/exp OR baby OR 'toddler'/exp OR toddler OR 'pregnancy outcome'/exp OR 'pregnancy outcome' OR 'pregnancy outcomes' AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim)	Jul 2, 2012	1,029,794
#11.26	placenta:de OR placental:de AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim)	Jul 2, 2012	36,205
#11.25	placenta:ti OR placental:ti OR placenta:ab OR placental:ab AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim)	Jul 2, 2012	39,369
#11.24	'placenta'/exp AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim)	Jul 2, 2012	25,579
#11.23	'breast milk'/exp OR 'breast milk' AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim)	Jul 2, 2012	10,992
#11.22	maternal AND [humans]/lim AND [english]/lim	Jul 2, 2012	156,803
#11.21	'nursing' AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim)	Jul 2, 2012	75,798
#11.20	'infant'/exp OR 'infant' AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim)	Jul 2, 2012	582,853
#11.19	pregnant OR 'fetus'/exp OR fetus OR fetal AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim) AND [2009-2013]/py	Jul 2, 2012	70,661
#11.18	'pregnancy'/exp OR 'pregnancy' AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim)	Jul 2, 2012	330,242
#11.17	'abnormalities'/exp OR abnormalities AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim) AND [2009-2013]/py	Jul 2, 2012	90,954
#11.16	'preterm birth'/exp OR 'preterm birth' OR 'birth defect'/exp OR 'birth defect' OR 'birth defects' AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim)	Jul 2, 2012	26,179
#11.15	'low birth weight'/exp OR 'low birth weight' AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim)	Jul 2, 2012	24,025
#11.14	'prenatal outcome' OR 'prenatal outcomes' AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim)	Jul 2, 2012	19
#11.13	prenatal AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim)	Jul 2, 2012	142,496
#11.12	#11.5 AND #11.11	Jul 2, 2012	1,165
#11.11	#11.6 OR #11.7 OR #11.8 OR #11.9 OR #11.10 OR 'adverse drug reaction':lnk OR 'drug toxicity':lnk	Jul 2, 2012	2,232,421
#11.10	'risk'/exp AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim)	Jul 2, 2012	722,208
#11.9	'mercury poisoning'/exp OR 'mercury poisoning' AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim)	Jul 2, 2012	1,265
#11.8	'poisoning'/exp OR poisoning AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim)	Jul 2, 2012	113,869
#11.7	'toxicity'/exp OR toxicity AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim)	Jul 2, 2012	408,749
#11.6	'adverse effect'/exp OR 'adverse effect' OR 'adverse effects' AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim)	Jul 2, 2012	241,347
#11.5	#11.1 OR #11.2 OR #11.3 OR #11.4	Jul 2, 2012	2,141
#11.4	'elemental mercury' OR 'mercury vapor' OR 'mercury vapors' OR 'mercury vapour' OR 'mercury vapours' OR 'hg vapour' OR 'hg vapor' OR 'hg vapors' OR 'metallic mercury' OR 'liquid mercury' AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim)	Jul 2, 2012	629
#11.3	mercury AND (dental OR dentist*) AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim)	Jul 2, 2012	1,153
#11.2	amalgam* AND (dental OR dentist* OR filling OR fillings) AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim)	Jul 2, 2012	958
#11.1	'dental alloy'/exp AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [embase classic]/lim)	Jul 2, 2012	533

2. Toxline database

The following are three groups of terms we used on July 3, 2012.

9 toxline(#7 NOT #8) 12:32:12 209
8 toxline(animal OR animals) AND (eng [la]) NOT PubMed [org] NOT pubdart [org] 12:31:15 319153
7 toxline(#5 AND #6) 12:29:51 482
6 toxline((prenatal OR prenatal outcomes OR low birth weight OR preterm birth OR birth defect OR birth defects OR abnormality OR abnormalities OR pregnancy OR pregnant OR fetus OR fetal OR infant OR nursing OR exposure OR maternal OR "breast milk" OR placenta OR placental OR "cord blood" OR child OR children OR baby OR newborn OR neonatal OR neonate OR preschool OR infancy OR toddler OR pregnancy outcome OR pregnancy outcomes OR neurodevelopment OR neurodevelop* OR neurotoxicity OR neurotoxic*)) AND (eng [la]) NOT PubMed [org] NOT pubdart [org] 12:29:17 204783
5 toxline(#3 AND #4) 12:28:43 973
4 toxline(#1 OR #2) 12:28:29 1236
3 toxline(("adverse effect" OR "adverse effects" OR "adverse event" OR "adverse events" risk OR toxicity OR "mercury poisoning" OR "poisoning")) AND (eng [la]) NOT PubMed [org] NOT pubdart [org] 12:27:30 442892
2 toxline(("elemental mercury" OR "mercury vapor" OR "mercury vapors" OR "mercury vapour" OR "mercury vapours" OR "hg vapour" OR "hg vapor" OR "hg vapors" OR "metallic mercury" OR "liquid mercury")) AND (eng [la]) NOT PubMed [org] NOT pubdart [org] 12:26:16 709
1 toxline((dental OR dentist* OR filling*) AND ((mercury OR "quecksilber german " OR "mercurio italian " OR "mercure french " OR "liquid silver" OR "kwik dutch " OR hydrargyrum OR "colloidal mercury" OR 7439-97-6 [rn]) OR amalgam*)) AND (eng [la]) NOT PubMed [org] NOT pubdart [org] 12:25:45 691

3. DART database

The following are three groups of terms we used on July 6, 2012.

3 dart(#1 OR #2) AND (eng [la]) NOT PubMed [org] 10:36:47 57
2 dart(("elemental mercury" OR "mercury vapor" OR "mercury vapors" OR "mercury vapours" OR "hg vapour" OR "hg vapor" or"hg vapors" OR "metallic mercury" OR "liquid mercury")) NOT PubMed [org] 10:35:15 47
1 dart((dental OR dentist* OR filling OR fillings) AND ((mercury OR "quecksilber german " OR "mercurio italian " OR "mercure french " OR "liquid silver" OR "kwik dutch " OR hydrargyrum OR "colloidal mercury" OR 7439-97-6 [rn]) OR amalgam*)) NOT PubMed [org] 10:34:23 31

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2014 Update

Purpose

The purpose of this memorandum is to present an UPDATE of the systematic literature review that was completed December 12, 2012 on risks associated with mercury (Hg) exposure from dental amalgam fillings for three sensitive groups:

1) Pregnant women and their developing fetuses
2) Children under six years of age
3) Women who are breastfeeding and nursing infants

Background/Objective

Dental amalgam is a dental restorative material used to fill cavities caused by tooth decay. It is a heterogeneous inter-metallic compound, consisting of elemental Hg (liquid) and amalgam alloy (powder) composed of primarily silver, tin, and copper. Approximately 50% of dental amalgam is elemental Hg by weight. Dental amalgam has been on the U.S. market in its present form since the 1890s and has been the predominant and clinically preferred material for restoring most posterior teeth (i.e., molars and premolars) [1].

Dental amalgam is a "pre-amendment device," which means that it was in use prior to May 28, 1976 when the FDA was given broad authority to regulate medical devices by law. The law required the FDA to issue regulations classifying pre-amendment devices according to their risk into class I, II, or III. The two components of dental amalgam, dental Hg and amalgam alloy, were initially classified as Class I and Class II devices separately in 1987. There are growing concerns about the Hg toxicity because the Hg vapor emitting from amalgam restorations can be absorbed by the patient through inhalation, ingestion, or other means [2]. To address these concerns, the Department of Health and Human Services (HHS), specifically U.S. Public Health

Service (USPHS) and the Food and Drug Administration (FDA), evaluated the relevant scientific literature regarding the health effects of dental amalgam and published their findings in the 1993 and 1997 USPHS Reports on Dental Amalgam [3, 4]. Scientists and health professionals from U.S. government agencies (CDC, EPA, NIEHS, NIDR, NIOSH, and FDA) and academia with diverse science backgrounds and expertise in toxicology, neurotoxicology, immunotoxicology, and epidemiology, contributed to the literature review for these two reports. These two reports concluded similarly that "current body of data does not support claims that individuals with dental amalgam restorations will experience adverse effects, including neurologic, renal or developmental effects, except for rare allergic or hypersensitivity reactions".

These reports also recommended a strategic plan for USPHS agencies for future research, education, and regulation of dental amalgam including, particularly, FDA was recommended to regulate elemental Hg and dental alloy as a single product, and to require manufacturers to disclose the ingredients of these materials in product labeling.

Milestones on FDA regulations related to dental amalgam or dental products, were as follows:

1) 1993-94 – Multiple Dental Products Panels:

- discussed the risks and benefits of dental amalgam,
- stated that there were no major risks associated with encapsulated amalgam, when used as directed, but recognized there was a small population of patients who may experience allergic reactions to the materials in the device, and
- recommended FDA reclassify the components of dental amalgam into a single class II regulation

2) August 2006 -- A joint committee of CDRH Dental Products Panel and CDER Peripheral and Central Nervous System Drugs Advisory Committee:

- discussed FDA's draft White Paper on the latest peer-reviewed literature on dental amalgam,
- identified gaps in the scientific knowledge, especially with respect to exposure limits and lack of attention to risk factors for sensitive subpopulations, and
- recommended FDA to conduct an even deeper review of the scientific literature on this topic.

3) July-Aug 2009 – Final Rule and Addendum to the 2006 White Paper [5]

- provided additional literature review and responses [6] to 2006 panel's comments and recommendations regarding 2006's draft White Paper. Essentially, there was insufficient evidence to support an association between exposure to Hg from dental amalgams and adverse health effects in humans, including sensitive subpopulations.
- issued a final Rule (21 CFR Part 872) [7] with a special control guidance document for dental amalgam and classified all components of dental amalgam (amalgam, Hg, and amalgam alloy) into Class II devices (21 CFR 872.3070)[8].
- The special controls recommended manufacturers, among other things, to add a specific labeling, including an "information for use" statement in the labeling and a performance test to determine the amount of Hg vapor released by a dental amalgam device during corrosion (ng/cm2 in 4 hrs).
- established a public-accessible website to provide dental amalgam related information (http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DentalProducts/DentalAmalgam/default.htm).

Since the issuance of the final rule in 2009, however, FDA had received petitions requesting a reconsideration of the rule. The petitioners raised myriad concerns, both scientific and administrative. Based on the concerns raised, the petitions requested that FDA either ban amalgam or place restrictions on its use, especially for pregnant women, children under six, and sensitive individuals. To respond to the petitioner concerns, FDA held an Advisory Panel meeting on December 14-15, 2010.

4) December 14-15, 2010 -- An advisory committee meeting on the human health risks of Hg vapor exposure from dental amalgam

- At this panel meeting a new risk assessment recommended by the expert consultation and the panel [9] and prepared by SNC-Lavalin, Inc., was presented. This assessment, for the first time, characterized Hg exposure from dental amalgam in the U.S. population by the number of filled amalgam surfaces and age group. Summarizing the results of this assessment, dental amalgam was the primary source of exposure to elemental Hg (Hg) in the general, non- occupationally exposed population, of which the fetus and young infant were considered to be vulnerable. Conservative estimates showed that >30% of children and >60% of adults with amalgam fillings in the U.S. were exposed to Hg from dental amalgam exceeding published RELs (EPA's RfC) for Hg vapor.
- Panel recommendations: The potential risks of Hg vapor exposure from dental amalgam need to be communicated to the public. Informed patient consent to treatment is important. FDA should consider warnings against use in sensitive groups, including pregnant women, young children, and those with kidney dysfunction or allergy to Hg.

To address the concerns of the petitioners and the advisory panel, an epidemiology systematic review of the published literature was conducted. The sensitive groups of interest are: (1) pregnant women and their developing fetuses, (2) children under six years of age; and (3) women who are breastfeeding and nursing infants. The objective of this review is to provide a systematic literature review on the risks associated with Hg exposure from dental amalgam fillings in each of the three sensitive subpopulations.

This literature review was completed December 12, 2012. ODE lead reviewer asked for an update of the 2012 literature review per center management request.

Methods

The below search strategy was replicated on June 29, 2014. The primary strategy involved the search of published literature in four electronic databases

(PubMed, Embase, Toxline, and DART), and employed the following search strings that were

slightly modified from 2006's White Paper [5]. Specifically, changes consisted of adding more terms for health outcomes (e.g. a list of adverse effects for fetuses, newborns, pregnant women and nursing mother), more databases (i.e. added non-indexed Medline, Embase, Toxline and DART databases), and deleted the limits of "Clinical Trials" and publication date ("from 2003 to 2006").

Pubmed database

The following are three groups of terms we used on June 29, 2014.

Search #1:

> (“Dental Amalgam"[MeSH] OR “(amalgam OR amalgam*) AND (dental OR dentist OR dentistry OR dentist* OR filling OR fillings)” OR “mercury AND (dental OR dentist OR dentistry OR dentist*)” OR "elemental mercury" OR "mercury vapor" OR "mercury vapors" OR "mercury vapour" OR "mercury vapours" OR "Hg vapour" OR "hg vapor" OR "hg vapors" OR "metallic mercury" OR "liquid mercury")

Search #2:

> #1 AND:
>
> ("adverse effects"[Subheading] OR "Risk"[MeSH] OR "toxicity"[Subheading] OR "Mercury Poisoning"[MeSH] OR "poisoning"[Subheading])
>
> Search #3:
>
> #2 AND
>
> (prenatal OR “prenatal outcomes” OR “low birth weight” OR “preterm birth” OR “birth defect” OR “birth defects” OR abnormality OR abnormalities OR pregnancy OR pregnant OR fetus OR fetal OR infant OR nursing OR exposure OR maternal OR
>
> "breast milk" OR placenta OR placental OR "cord blood" OR child OR children OR baby OR newborn OR neonatal OR neonate OR preschool OR infancy OR toddler OR “pregnancy outcome” OR “pregnancy outcomes” OR neurodevelopment OR neurodevelop* OR neurotoxicity OR neurotoxic*)

Then, limit Species to “Humans”, publications to be “English” with “Abstract”.

This yielded 34 articles.

Eligibility criteria: Searches were limited to articles published in English with Hg exposure stemming from dental amalgam and published from July 2, 201 (when last search was performed for 2012 literature review) to June 29, 2014.

Study Selection: included articles for full text review were selected only if they met the following criteria:

1. articles that evaluated the correlations and/or health effects(risks) of dental amalgam in one of the three sensitive groups;
2. all original research articles
3. case series with greater than nine subjects;

4. literature reviews, in which the review process was conducted in a systematic manner with clear definition of terms/key words used to search databases and a clear screening process was described.

Data collection process: The abstracts were first reviewed and screened to identify articles that will go through full text review. Then, the full text review articles were assessed per the eligibility for inclusion/exclusion (Figure 1) and the study results. The study results from the final articles were extracted and tabulated into two tables (Tables 1-2).

Data items: Due to the specific interests of the subpopulations of this literature review, the following data variables were summarized into detailed results (Table 2): first author's last name, study design, study population (list age when possible), sample size, study endpoints, Hg source (e.g. dental amalgam, food consumption), Hg sample measured(e.g. urine, hair, blood), results/conclusion.

Summary of Results:

Overview of Studies

A full diagram of article retrieval and selection appears in Figure 1. In summary, the above search yielded 34 articles from PubMed. The 34 were initially screened to exclude studies not pertaining to dental amalgam studies, with no mention of assessments of health risks and not include any of the three sensitive groups.

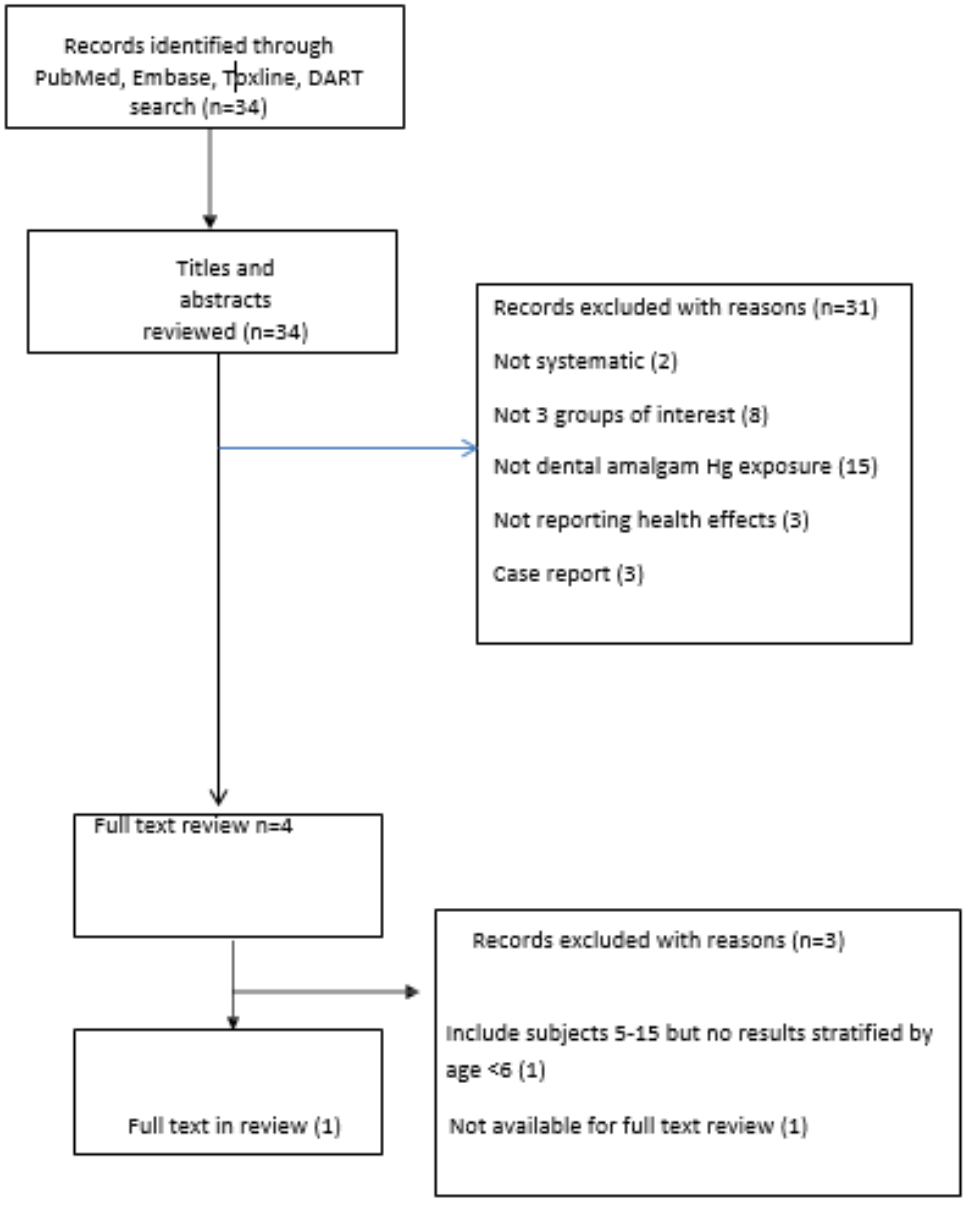
31 articles were excluded during the initial screening for the following reasons: case report (n=6), dental restoration only (n=2), reporting on measurement techniques of Hg (n=2), describing dental Hg hypersensitivity reactions (n=1) human studies but none specified 3 groups (n=8), non- systematic review article (n=2), not dental amalgam Hg exposure (n=15), had children less than 6 years old but did not have results stratified by age (n=1) and 1 case where full text articles were not available at the time of writing this review.

A brief description of the article1 that was obtained during this update is as follows:

It was a prospective cohort study of 300 pregnant women in the Republic of Seychelles, that evaluated prenatal mercury vapor exposure during gestation from dental amalgam was associated with cognition and development in children. Outcomes were the child's mental (MDI) and psychomotor (PDI developmental indices of the Bayley Scales of Infant Development-II (BSID-II) administered at 9 and 30 months. Complete exposure, outcome, and covariate data was available on a subset of 242 mother–child pairs.

Results showed that there was no significant difference with PDI or MDI scores among children who were exposed during gestation to mercury from dental amalgam. A secondary analysis of 9-month MDI showed a slight adverse association among girls.

Figure 1 Flow diagram of article retrieval and selection



Critique and Assessment

The above study is a prospective study that included strong and reliable methods of amalgam exposure and validated neurodevelopmental endpoints. The study also contained substantial information on other potential co-variates that were defined a priori as potential cofounders in the adjusted analysis. One potential confounder that was not able to be adjusted for in this analysis was selenium (Se) consumption which is found in high concentrations in fish consumed in Seychelles. Se has been shown

to be protective of MeHg toxicity so results of this study might not necessarily be generalizable to populations that do not have high concentrations of Se within their diets. Finally, results were limited to testing children at 9 and 30 months, further evaluation of these children at a later age when sensitivity of testing is increased would be necessary for consistency and persistence of any associations.

Conclusions:

The updated literature review further corroborates the findings that were found in 2012, there were no association between prenatal Mg exposure and cogitative impairments in children.

It should be noted that many of the articles that were excluded in this update were excluded because they reported on associations of prenatal Hg exposure and outcomes among children greater than 6 years old. There could be more literature and evidence that points to associations that were not evaluated here.

Reference

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Abbreviations

ALSPAC	- Avon Longitudinal Study of Parents and Children
ANA	- Antinuclear antibodies
ASD	- Autism spectrum disorder
ASIA	- Autoimmune/inflammatory syndrome induced by adjuvants
CI	- Confidence interval
CDC	- Centers for Disease Control and Prevention
CVAAS	- Cold vapor atomic absorption spectrophotometry
CVAFS	- Cold vapor atomic fluorescence spectroscopy
Hg	- Hydrargyrum (mercury)
HLA-DR	- Human leukocyte antigen DR
HR	- Hazard ratios
HRR	- Heart rate recovery
ICP-MS	- Inductively coupled plasma–mass spectrometry
LST, or LTT	- Lymphocyte stimulation, or transformation, test
MeHg	- Methylmercury
MCS	- Multiple chemical sensitivity
MRI	- Magnetic resonance imaging
NHANES	- National Health and Nutrition Examination Survey
OL(C)R	- Oral lichenoid (contact) reaction
OLL	- Oral lichenoid lesion
OLP	- Oral lichen planus
Ppb	- Parts per billion
Ppm	- Parts per million
RBC	- Red blood cells
SCC	- Squamous cell carcinoma
SCENIHR	- Scientific Committee on Emerging and Newly-Identified Health Risks
SLE	- Systemic lupus erythematosus
WHO	- World Health Organization