Dental Amalgam

Background

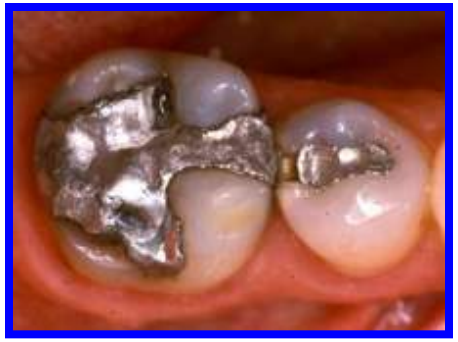
Michael E. Adjodha, M.ChE.
Acting Assistant Director,
Restorative and Surgical Dental Devices Team
Division of Dental Devices
OHT1/OPEQ/CDRH

Outline

- Amalgam Characteristics
- Agency Assessments

What is Dental Amalgam?

- A dental restorative material used for filling carious defects in teeth
- Comprised of 1:1 mixture of elemental mercury (Hg°) and powdered silver-tin-copper alloy; marketed in encapsulated form
- Mercury and powdered alloy mixed at point of care to form plastic mass; hardens *in situ* to form a solid substance
- Domestic use
  - On U.S. market in present form since the late 1800s
  - Approximately 50 million amalgam restorations placed annually in U.S.
  - Less than 40% of all direct restorations placed
  - Use declining 2-4% annually in U.S.
- Alternatives:
  - Composite resins (for all classes of restorations)
  - Glass ionomer cements (for small restorations)

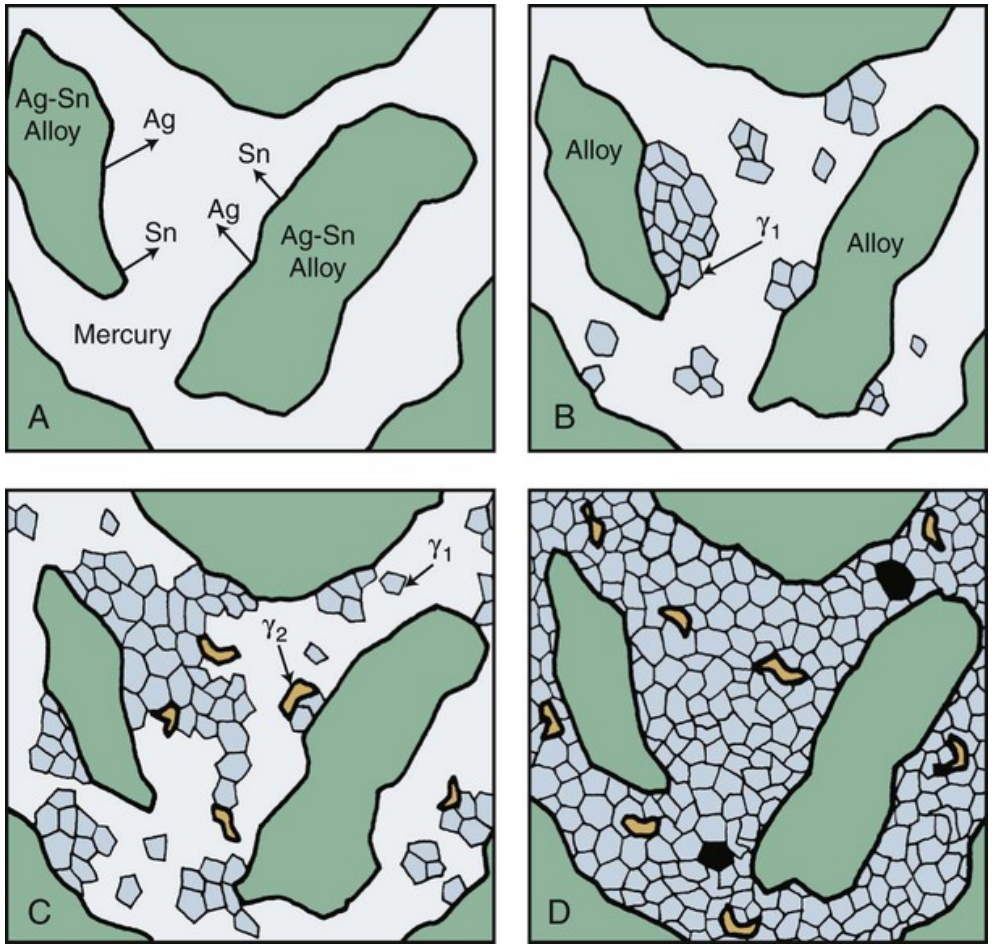


Amalgam Characteristics

- Advantages:
  - High strength
  - Suitability for all classes of restorations
  - Good marginal integrity
  - Durability
  - Ease of use
  - Affordability

- Disadvantages:
  - Releases mercury vapor
  - Poor aesthetics
  - Requires larger tooth preparations
  - Susceptible to corrosion

Mercury in Dental Amalgam



Source: Philips' Science of Dental Materials, 2003

Mercury Vapor

- After setting, dental amalgam can release mercury vapor, particularly under mechanical stress, abrasion, and elevated temperatures
- Release from
  - Residual unreacted mercury in the matrix
  - Corrosion of intermetallic tin and copper phases
- Main route of patient and occupational exposure is via inhalation
  - inorganic mercury is poorly absorbed through GI tract

Assessments

- 1993 Public Health Service (PHS) Report
- 1997 Update to PHS Report
- 2004 Life Sciences Research Office Report (NIH)
- 2009 FDA White Paper
- 2009 FDA Final Rule
- 2010 FDA Mercury Allergy Review
- 2010 FDA Systematic Literature Review
- 2012-2014 FDA Literature Review of Potentially Sensitive Subpopulations
- 2015 FDA Response to Citizen Petitions
- 2019 FDA Systematic Epidemiologic Literature Review

1993 Public Health Service (PHS) Report

Multi-agency literature review by HHS, Subcommittee on Risk Management/Committee to Coordinate Environmental Health and Related Programs (CCEHRP)

- Findings:
  - Daily mercury dose higher for subjects with 7 to 10 amalgams than for persons with no amalgams
  - Available data not sufficient to indicate that health hazards can be identified in non-occupationally exposed persons
  - Evidence not persuasive that wide variety of non-specific symptoms attributed to the fillings and "improvement" after removal were attributable to mercury from dental amalgam
  - However, the evidence was not persuasive that the potential for toxicity at the levels attributable to dental amalgams should be totally disregarded
- Concluded that mercury released from amalgam does not pose a serious health risk to the general public

1997 Update to PHS Report

- Multi-agency update to 1993 PHS report
  - Included a review of additional 150 studies submitted in citizen petitions
- Findings consistent with the earlier assessment
  - Mercury is a well-known toxicant,
  - Toxicity is dependent on dose,
  - Mercury from amalgam fillings can accumulate in tissues
- Data was insufficient to conclude that patients with dental amalgam restorations will experience adverse health effects, including neurologic, renal, or developmental effects

2004 LSRO Report (NIH)

- Review of 300 studies published from 1996 through 2003
- Report concluded:
  - 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
  - Data did not support a causal association between mercury release from dental amalgam and other non-specific complaints that have been attributed to this restoration material

2009 FDA White Paper

- 2006 -- FDA prepared Draft White Paper on the potential adverse health risks associated with exposure to mercury in dental amalgam
  - presented at FDA advisory committee meeting; panel recommended FDA revisit to address research gaps
- 2009 -- FDA addressed the gaps and finalized the paper with an Addendum
  - final White Paper contained FDA review of amalgam literature published since 1997 and found no new information that would change conclusions of earlier assessments
- The conclusions were used to support the findings of the Final Rule
  - 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
  - Clinical data are limited regarding certain sensitive subpopulations (pregnant women and their developing fetuses, and children under six, including breast fed infants)

2009 FDA Final Rule on Dental Amalgam

The final rule combined amalgam alloy and mercury components of dental amalgam into a single Class II classification regulation and established special controls (performance data and labeling)

- 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
- Found with respect to potentially sensitive populations, i.e., fetuses, breastfed infants, and children under six years of age, no adverse effects are expected but clinical data are limited
- Concluded that exposures to mercury vapor from dental amalgam are not associated with adverse health effects in the general population age six and older

2010 FDA Review of Mercury Allergy Literature

- Peer-reviewed literature was assessed to determine the definition, diagnosis, and genetic predisposition to mercury allergy
- Findings:
  - Mercury allergy typically takes the form of localized, delayed-type, cell-mediated cutaneous or mucosal reactions
  - 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 Epidemiologic Literature Assessment

- To determine if there was new information since the final rule concerning associations between mercury vapor exposure and adverse health outcomes
- Findings:
  - Number of dental amalgam fillings and surfaces correlate with mercury content in kidney, urine, saliva, and hair
  - Correlation exists between the number of maternal amalgam fillings and increased mercury levels in maternal blood, follicular fluid, and cord blood
  - Dental occupational exposure to mercury 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 reported allergic or immune responses to mercury (e.g., oral lichenoid reactions); many of these symptoms resolved after removal of amalgam fillings
  - Children exposed to dental amalgam had urine protein content (microalbuminuria) and small increases in the urine concentrations of porphyrins
- Conclusions:
  - None of the reviewed studies provided evidence of causality
  - Available findings were limited by the lack of proper controls, small sample sizes, length of follow-up, and lack of mercury speciation analysis

2012 -2014 FDA Assessment – Potentially Sensitive Subpopulations

- Focused on articles that evaluated possible risks from exposure to mercury from dental amalgam among the following sensitive groups: pregnant women and their developing fetuses; children under six years of age; nursing women and breastfed infants
- Available studies on pregnant women and their developing fetuses or newborns reported inconsistent correlations between maternal dental amalgam and mercury levels in breast milk or in biofluids from breastfed infants and young children
- Overall, there was a lack of evidence that maternal dental amalgam increases the risks of health outcomes in pregnant and nursing women, their developing fetuses or breastfed newborns, and children under six years of age

2015 FDA Response to Citizen Petitions

- Several Citizen Petitions filed before and after 2009 final rule
- FDA held Advisory Committee meeting in 2010 to discuss the scientific issues raised in the petitions, i.e., exposure assessments, mercury vapor reference exposure levels (RELs), and the adequacy of the clinical studies for dental amalgam
- The panel discussed that there may be certain populations that are more sensitive to mercury exposure than the general population but that there is no causal link between the use of dental amalgam and various clinically-manifested conditions in the general population
- FDA considered the information provided by the panel, the comments to the docket, the available literature, and exhibits provided in the petitions and concluded in its response to the petitions in 2015:
  - 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

2019 Assessment

- The current assessment will serve as the basis for discussion at this Advisory Committee meeting to determine if there is new evidence related to the benefit/risk profile of dental amalgam
- Unlike the previous literature reviews (2010 -2015) which were limited to amalgam-attributed health outcomes, the current systematic assessment is aimed to provide a wider evaluation not restricted to certain health outcomes or vulnerable populations


FDA
U.S. FOOD & DRUG
ADMINISTRATION

U.S. FOOD & DRUG ADMINISTRATION

Dental Amalgam Report:

Systematic Literature Review on the Risk from Exposure to Dental Amalgam Related Mercury

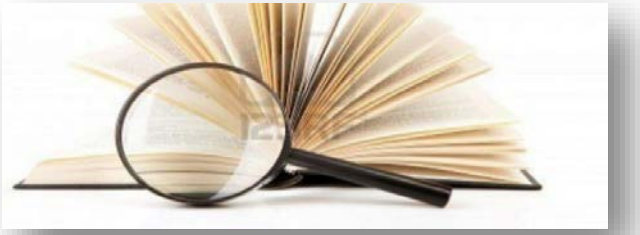
November 13, 2019: Immunology Devices Panel of the Medical Devices Advisory Committee Meeting

Yelizaveta (Lisa) Torosyan, MD, PhD

Systematic Review of Published Evidence on Dental Amalgam: *Aims and Search Strategy*

- Unlike some previous assessments, the current report presents an overview on *overall* safety of mercury from dental amalgam:
  - ***not*** limited to specific adverse outcomes *(e.g.,* neuro- or nephrotoxicity*)*
  - ***not*** limited to specific vulnerable subpopulations (*e.g.,* pregnant women, children)

- **The current review was aimed to identify *all* possible adverse outcomes that were reported within the last decade in relation to either occupational or non-occupational exposure to dental amalgam**



Systematic Review of Published Evidence on Dental Amalgam:
Article Retrieval and Selection in the Main Review

PubMed searches as of Sep 24, 2018:

PubMed 1st search, n=353/34,663 records:
"Dental Amalgam"[Mesh] OR "Mercury"[Mesh] OR "Mercury Poisoning, Nervous System"[Mesh] OR "Mercury Poisoning"[Mesh] OR "silver mercury amalgam" [Supplementary Concept] OR "Contour (dental amalgam)" [Supplementary Concept]

PubMed 2nd search, n=222/11,124 records:
(dental OR dentist* OR filling*) AND (amalgam* OR mercury OR "Hg vapor*" OR "Hg vapour*")

Combined PubMed search, n=405 records (see Figure 2 below)

EMBASE searches as of Sep 25 and Oct 5, 2018:

EMBASE, n=915/10,590 records:
Sources: Embase, Embase Classic, MEDLINE Query: ('dental'/exp OR dental OR dentist* OR filling*) AND (amalgam* OR 'mercury'/exp OR mercury OR 'hg vapor*' OR 'hg vapour*') AND [article]/lim AND [english]/lim AND [humans]/lim AND ([embase]/lim OR [medline]/lim OR [embase classic]/lim) AND [2010-2018]/py Mapped terms: ''mercury'' mapped to 'mercury', term is exploded

EMBASE/PICO, n=40/388 records (see Figure 3 below)

Records **excluded** using search filters (n=55,235):
- Full text
- Humans
- English
- Date: 2010/01/01 – 2018/12/31
- Clinical studies and case reports

PubMed 1st search: n=34,310
PubMed 2nd search: n=10,902

EMBASE search: 9,675
EMBASE/PICO search: n=348

1st pass:
Titles and abstracts reviewed from all PubMed and EMBASE searches: n=1,360

1st pass records **excluded** manually (n=1,160):
- Replicate findings in PubMed/EMBASE searches
- Not original study or case report
- Dental restorations not specified as amalgams
- Not relevant outcomes (*e.g.*, effectiveness and not safety)

2nd pass:
Full-text articles assessed for eligibility as original studies (epidemiologic, clinical and preclinical) and case reports on dental amalgam-related (occupational and non-occupational) Hg levels, toxicity outcomes, and susceptibility markers (n=200)

2nd pass records **excluded** manually (n=21):
- See the exclusion criteria listed above

Studies included in final qualitative evidence synthesis (n=185)

Cross-references (n=6)
FDA 2010 review: *Dunn et al 2008, Geier et al 2009,* and *Palkovicova 2008*
SCENIHR 2015 review: *Mackert 2010, Montebugnoli et al 2012,* and *Warwick et al 2013*

Contents of the Main Review (Jan 2010 – Sep 2018):

Summary and Two Appendices with Individual Reviews (>230 references)

Contents

Addendum: Review Update on the Literature Published between Sep 2018 and Aug 2019 *(>20 references)*

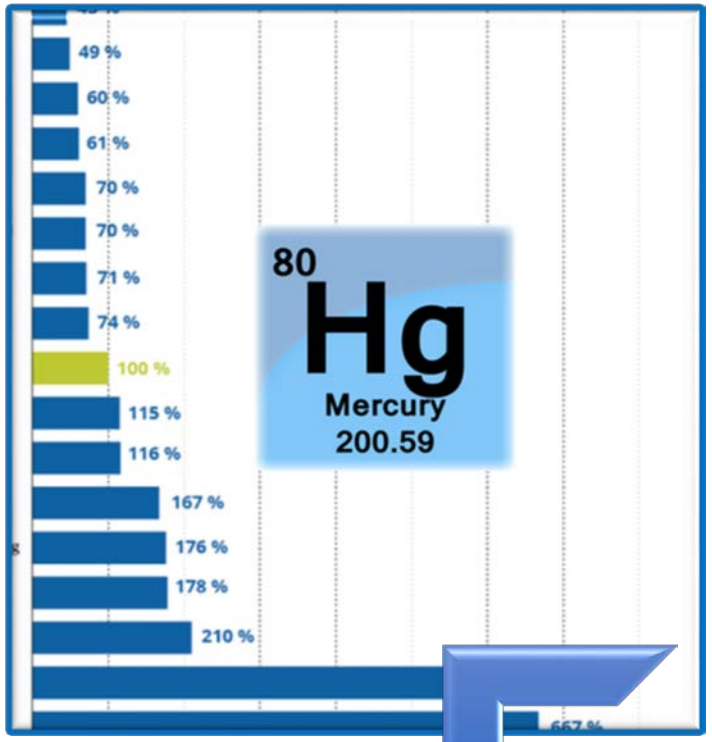
Note: On the slides, the main review references are indicated by numbers in square brackets []; the supporting references and the Addendum references are indicated by author names and publication years.

Varying Evidence on Different Amalgam Related Outcomes

- ***Strong*** evidence on increased mercury levels:
  - Positive correlations with amalgam fillings in multiple studies
  - Decreased urine concentrations among children due to the restricted use of dental amalgam (Germany, since 1992)
  - However, dose-response relationships affected by:
    - *Interindividual variability?*
    - *Inaccurate measurements due to methodological limitations?*

- ***Moderate*** evidence on oral mucosa/cutaneous manifestations in many studies (*e.g.,* amalgam tattoo, oral lichenoid lesions, oral granulomatosis)

- ***Inconclusive*** evidence on non-local (systemic) outcomes in single studies (*e.g.,* Parkinson's disease, multiple sclerosis, tremor)



Increased Mercury Levels

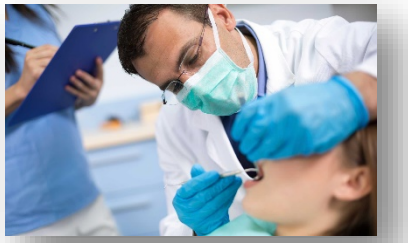
as the Main Subclinical Outcome Attributable to Dental Amalgam

Mercury Levels due to *Non-Occupational* Exposure to Dental Amalgam

- **Positive correlations between mercury levels and the number of amalgam fillings or surfaces in most studies on *adult* and *pediatric* populations**
- Per National Health and Nutrition Examination Surveys (NHANES 2003–2004 and 2010–2012) [33], geometric means of blood total Hg and inorganic Hg in the US population correlated with numbers of dental surface restorations (DSRs grouped as 0, 1–8 and >8; *note: amalgam vs. composite resin fillings were not specified*):
  - 2003-2004: **Total Hg** - 0.48, 0.69 and 1.17 µg/L; **Inorganic Hg** - 0.32, 0.33 and 0.39 µg/L
  - 2010-2012: **Total Hg** - 0.51, 0.69 and 0.99 µg/L; **Inorganic Hg** - 0.20, 0.22 and 0.29 µg/L
- Only a few studies reported no association between dental amalgam exposure and mercury levels in body tissues or fluids:
  - Relatively small sample sizes
  - Unconventional biospecimens
- An overall decrease of mercury levels attributed to reduced use of dental amalgam over the last decades (Germany, Sweden, US)

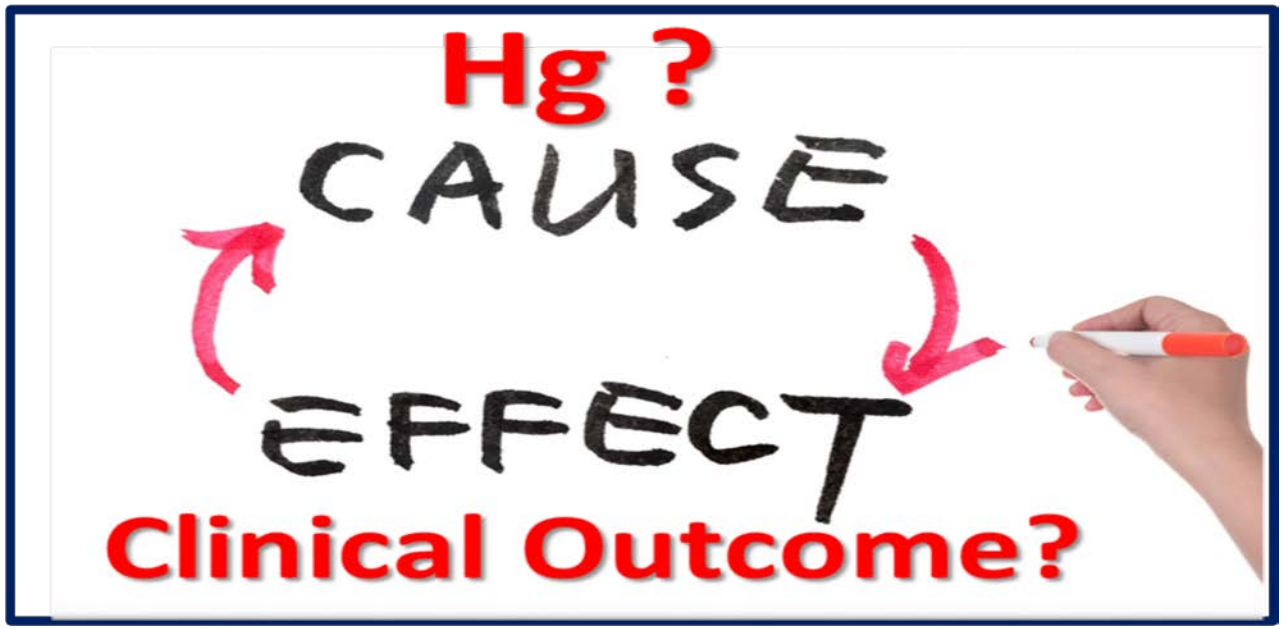
Further Evidence from Studies Assessing Mercury Levels at Populational Levels

- Model-based studies [179, *SNC-Lavalin Environment group & GM. Richardson (2010)*:
  - Per lowest predicted levels of dental amalgam exposure, 67.2 million Americans may exceed the US EPA reference level for inhalation of elemental mercury vapor
  - About 101.5 million Americans may exceed urine mercury concentration per reference exposure level of 0.06 ug/m^3 (Canada)
- **US or Canadian studies based on *actual mercury measurements* did not confirm high mercury levels attributable to dental amalgam:**
  - Urine mercury levels too low to pose health risks, per thresholds from Health Canada and German Federal Environment Agency [37, Canada]
  - Average blood mercury levels in the populationally representative US study were below WHO and US EPA thresholds [33, see the previous slide]
  - Per New York state and national NHANES surveys (2003-2004 and 2013-2014), the proportion of NY adults with **blood** mercury levels of ≥5 µg/L declined from 24.8% to 12% within the 10-year study period; only two study participants exceeded the reportable **urine** mercury level of 20 µg/L [*McKelvey 2018, Addendum*]

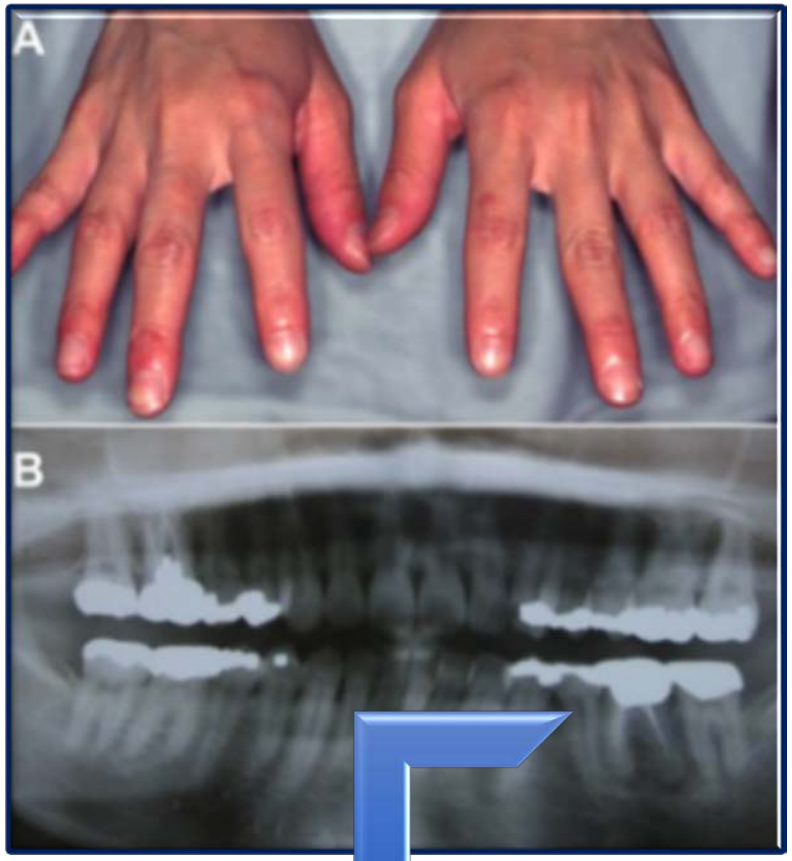


Mercury Levels due to *Occupational* Exposure to Dental Amalgam

- Positive associations between mercury concentrations and factors such as:
  - Duration of working in dental practice
  - Number of placed/removed amalgams and personal amalgam fillings
  - Use of heated copper amalgam or reusable capsules *vs.* encapsulated amalgam
  - Non-standard practices, *e.g.,* use of squeeze cloths
- Global (*geographic?/socioeconomic?*) variations :
  - A gradual decrease of mercury levels in developed countries since the 1960s-1970s [80, Norway]
  - Up to 30 µg/L in blood samples from certain locations (Lahore) [83, Pakistan]
  - Mercury levels among US professionals in comparison to the general population [69]:
    - Urinary mercury concentrations among US dentists decreased by 90% 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
    - However, urinary mercury levels among US dentists in 2011-2012 were still higher compared to the NHANES survey population: **1.69 µg/L** (95% CI: 1.58; 1.81) and **0.66 µg/L** (95% CI: 0.54; 0.78), respectively
- Dental training as potential source of high exposure:
  - 36% of the mercury vapor readings exceeded the absolute ceiling value when neither water spray nor high-volume suction was used during amalgam removal [82; *Warwick 2019, Addendum*]



Mercury Levels in Biofluids May Not Always Correlate with Other Clinical Manifestations Attributable to Dental Amalgam



[114], *Ko et al 2014*

Oral Mucosa and Skin Lesions

as Clinical Outcomes Attributable to Dental Amalgam

Amalgam Tattoo and Other Mucosal/Cutaneous Lesions:

Relatively Frequent Among Other Manifestations Yet Not Specific to Dental Amalgam

Figure 1. Clinical features: A blue-black macule was seen on the floor of the oral cavity adjacent to a restored tooth with dental filling.

Amalgam Tattoo [97]
(Amano et al 2011)

Figure 3: (a) Oral lichenoid lesion adjacent to amalgam and extending beyond it. (b) Complete healing after 6 months of replacing amalgam restorations

Oral Lichenoid Lesions with resolution after amalgam removal [108]
(Sharma et al 2015)

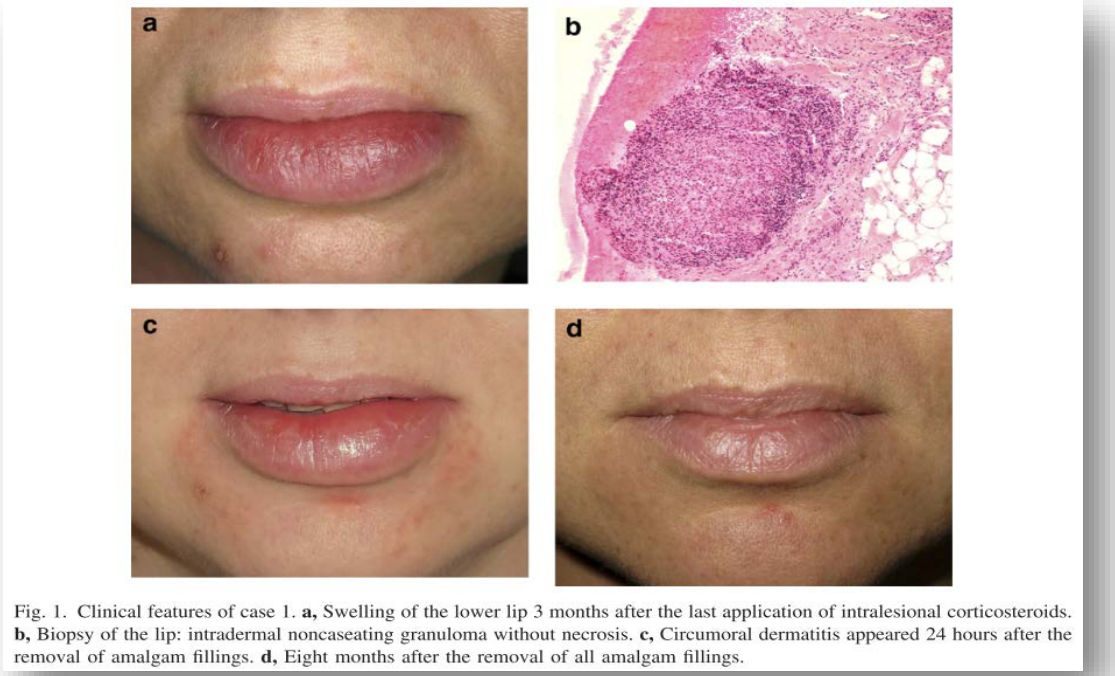
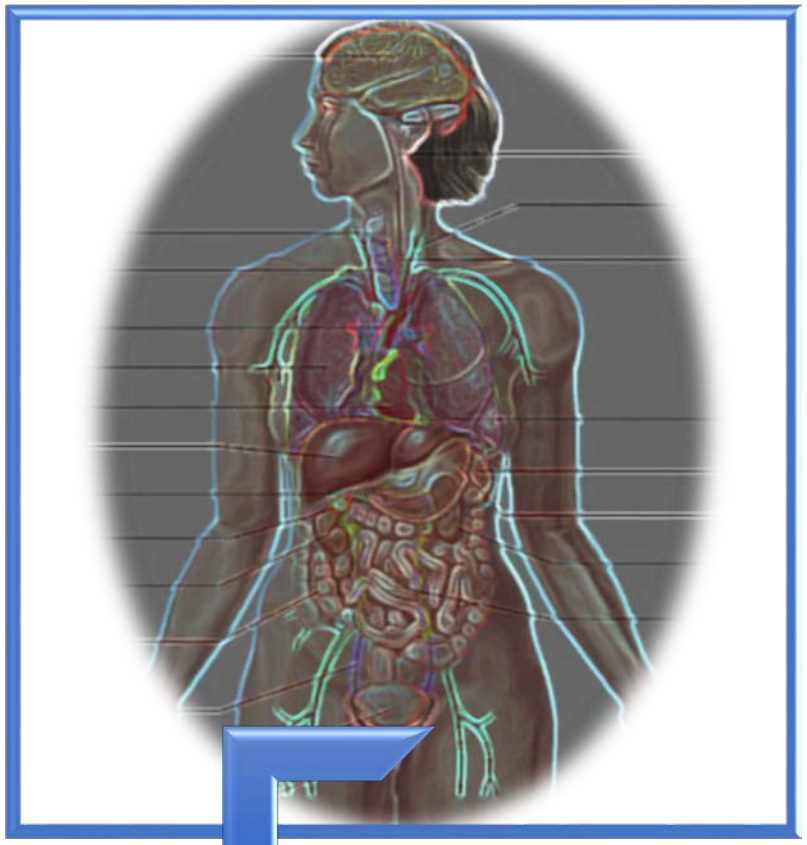


Fig. 1. Clinical features of case 1. **a,** Swelling of the lower lip 3 months after the last application of intralesional corticosteroids. **b,** Biopsy of the lip: intradermal noncaseating granuloma without necrosis. **c,** Circumoral dermatitis appeared 24 hours after the removal of amalgam fillings. **d,** Eight months after the removal of all amalgam fillings.

Orofacial Granulomatosis, including transient local dermatitis after amalgam removal [116]
(Tomka et al 2011)



Systemic Clinical Manifestations

as the Most Unclear Outcomes Attributable to Dental Amalgam

Varying Evidence on Neurological Outcomes in Relation to *Occupational* Exposure to Dental Amalgam

Positive Evidence:

- Memory loss, insomnia, tingling, and numbness as most frequent cognitive and neurological complaints among dentists (n=29); some correlations with exposure time or number of placed amalgam fillings [71, Brazil]
- More frequent self-reported symptoms such as memory problems, anxiety among dentists (n=64) vs. controls; tremor in dentists with urinary mercury >35 µg/g-creatinine [70, Tunisia]

Equivocal Evidence

- No clinically meaningful associations with multiple sclerosis – MS [69, US]:
  - however, MS prevalence was calculated as 183 per 100,000 among US dental professionals, compared to the referenced estimate of 130 per 100,000 in the general US population
  - A slightly increased risk trend for tremor was linked to cumulative mercury exposure and higher urine mercury levels

Negative evidence:

- No changes in motor and memory-related functions in female personnel [133, Norway]
- Similar or *higher* cognitive function among adult sons of female dental workers *vs.* matched controls [134, Sweden]
- No elevated risks for neurological diseases or intellectual disability among sons of female dental *nurses* [135, Sweden]
- No changes in peripheral nerve function [72, US]

Varying Evidence on Neurological Outcomes in Relation to *Non-Occupational* Exposure to Dental Amalgam

Positive Evidence:

- Increased risk trends for:
  - ADHD among young individuals with ≥6 amalgam restorations: HR=1.20, 95% CI=1.04-1.38 [*Lin 2018, Taiwan; Addendum*]
  - Alzheimer's disease among subjects with *vs.* without amalgam fillings: OR=1.105 (95% CI: 1.025, 1.190) [40, Taiwan]
  - Parkinson's disease among subjects with *vs.* without amalgam fillings: HR=1.58, 95% CI: 1.12, 2.23 [138, Taiwan]
  - Restless legs syndrome: OR=1.20; 95% CI: 1.02, 1.42 [*Szklarek and Kostka 2019, Poland; Addendum*]
- Subclinical: decrease of the tomographically assessed inner plexiform layer volume in relation to blood mercury levels and BMI [*Bilak 2018, Turkey; Addendum*]

Equivocal Evidence

- Changes in Expanded Disability Status Scale scores among patients (n=33) with multiple sclerosis [136, Romania]
- Self-assessed symptoms (mainly musculoskeletal and neuropsychological); no difference in cognitive tests between amalgam and control groups [137, Sweden]

Negative evidence:

- No increased risk for amyotrophic lateral sclerosis [*Parkin Kullmann and Pamphlett 2018, Australia; Addendum*]

Nephrotoxicity of Mercury from Dental Amalgam:
Limited to Subclinical Outcomes

Equivocal Evidence on renal function markers:

- Urine N-acetyl-β-D-glucosaminidase as the most sensitive marker indicating that amalgam-related low-level exposure to mercury from amalgam fillings may affect renal tubular function in children [18]
- Based on New England Children's Amalgam Trial [163]:
  - No associations between N-acetyl-β-D-glucosaminidase (and two other markers) and amalgam or resin composite restorations
- Based on Casa Pia Dental Amalgam Clinical Trial [164, 165]:
  - Dose-dependent correlations between cumulative exposure to amalgam-related mercury and mercury bioburden associated porphyrins (pentacarboxyporphyrin, precoproporphyrin, and coproporphyrin)
  - Glutathione-S-transferase-**α** as a candidate marker indicative of amalgam-related damage in the *proximal* tubules where mercury is expected to accumulate (but not glutathione-S-transferase-**π** which is indicative of distal tubules function)

Dental Amalgam Related Systemic Inflammation/ Autoimmunity: *Possible Events with Unclear Causality*

Equivocal Evidence from patients diagnosed with:

- Symptoms indicative of chronic mercury toxicity [38]:
  - Autoimmune diseases reported more frequently in the group with >10 amalgams *vs*. 6-10 or 0-5 amalgams
  - Higher blood and urine mercury levels in subjects with autoimmune disorders and multiple sclerosis; correlations between amalgam fillings and mercury levels disappeared after adjusting for age and sex
- Multiple Chemical Sensitivity [39]:
  - Increased metal allergy by patch testing and LTT, along with higher mercury levels
- Case reports referring to Autoimmune/Inflammatory Syndrome Induced by Adjuvants (ASIA), sarcoidosis, chronic fatigue syndrome, fibromyalgia, and connective tissue diseases

Negative Evidence on *autoimmunity-related* clinical and subclinical outcomes:

- Systemic Lupus Erythematosus, SLE [123]: No associations between urine mercury and disease activity or damage; *negative* correlations between hair mercury and both SLE indices
- Hashimoto disease [124]: No difference regarding amalgam fillings
- No associations between oral metal exposure (amalgam) and serological phenomena [125]
- In the NHANES-based study, 16% of women of reproductive age were positive for antinuclear antibodies (ANA); ANA positivity was associated with higher levels of hair and blood (but not urine) mercury, suggesting the role of dietary methylmercury (but not amalgam-related mercury) in subclinical autoimmunity [126]

Other Outcomes Attributed to Dental Amalgam Exposure

Equivocal Evidence

- Single source and/or small size studies on:
  - Self-assessed health complaints
  - Health-related measures (*e.g.,* hospital discharges)
  - Cardiovascular outcomes (*e.g.,* risk of stroke or myocardial infarction)
  - Thyroid hormonal status among mother-child pairs
  - Lab test changes (*e.g.,* hemoglobin, cholesterol, aspartate/alanine aminotransferases)
- Conflicting evidence on markers related to oxidative stress and antioxidant system:
  - *Increased* plasma levels of superoxide dismutase-1 and glutathione (reduced form) due to non-occupational exposure [166]
  - *Decreased* blood levels of superoxide dismutase (and glutathione peroxidase) due to occupational exposure [77]
  - Inverse correlations between urine mercury and thioredoxin reductase-1 among chlor-alkali plant workers [76]
- *Ex vivo* genotoxicity testing:
  - No signs of genotoxic damage, except higher levels of condensed chromatin [167]
  - No DNA damage by comet assay, but some genotoxic damage in relation to both amalgam and resin composite fillings per micronucleus test [169]

Dental Amalgam Exposure in Children

Perinatal Exposure to Maternal Dental Amalgam:
Possible but Overlapping with Other Exposure Sources

- **Positive correlations** between maternal amalgam and mercury increases in biofluids from mother and child *(e.g.,* cord or venous blood, breast milk)
- Additional role of dietary and/or unconventional exposure:
  - In the predominantly Caribbean immigrant population (Brooklyn, NY), about 16% of cord blood mercury levels exceeded the estimated equivalent of US EPA reference dose (5.8 µg/L) [55]:
    - Fish consumption and mother's foreign birth as predictors of *cord blood* mercury
    - Amalgam fillings, mother's foreign birth, and use of mercury-containing special products as predictors of *urine* mercury

- **Negative** [153, 155) or **Equivocal** [154] evidence on developmental outcomes from *non-occupational* exposure
- An increasing risk trend for perinatal death among offspring of women with ≥13 amalgams, but possible role of residual or unknown confounding after adjustment (*Björkman et al 2018, Norway, Addendum*)
- Changes in the occurrence of infant allergy and respiratory symptoms (*Emeny et al 2019, US; Addendum*)
- Variability in outcomes from *occupational* exposure:
  - Higher urine mercury levels and more frequent spontaneous abortions and preeclampsia among Egyptian female dental professionals, with the offspring being smaller for gestational age [73]
  - No increased occurrence of congenital malformations or other pregnancy-related adverse outcomes (*e.g.,* low birth weight, preterm birth, small for gestational age, *etc.*) among Norwegian female dental personnel compared to the general population [152]

Autism as the Most Investigated Potential Neurotoxicity Outcome Among Children

Equivocal Evidence

- An increasing trend for mercury levels in relation to maternal amalgam fillings did not reach significance in a study that showed a statistical difference in hair mercury levels among autistic children *vs.* controls [140]
- Maternal amalgam fillings associated with presumably more severe autistic disorders [11]:
  - Children born from mothers with ≥6 amalgams during pregnancy had 3.2 times greater odds of being diagnosed with autism (as a severe form) vs. ASD (as a mild form), compared to children born from mothers with ≤5 amalgams
- Higher plasma mercury levels among children with ASD *vs.* controls speculatively attributed to prenatal amalgam exposure, based on a higher frequency of current maternal amalgams [139]

Negative Evidence:

- Elevated levels of some urinary porphyrins in autistic *vs*. neurotypical children, but no differences in current urinary mercury levels or past mercury exposure including both personal and maternal amalgams [141]
- No differences in urinary mercury levels among ASD children vs. controls, regardless of amalgam fillings [142]
- No evidence on adverse effects of prenatal mercury exposure in children with autism; increased maternal exposure to amalgam was associated with *lower* rates of poor sociability; poor social cognition was found among children whose mothers did not eat fish [143]
- No links to autism/ASD in subjects with dental amalgams; autistic/ASD children were reported to eat less fish [144]

Other Neurotoxicity Outcomes in Relation to Dental Amalgam Exposure in Children

Negative/Equivocal evidence:

- No differences pertaining to blood mercury levels or maternal dental fillings among children with motor and mental developmental disabilities, epilepsy, attention deficit/ hyperactivity disorder and autism, compared to healthy controls [145; *Lygre et al 2018, Norway; Addendum*]
- No meaningful differences in neuropsychological and psychosocial outcomes in children bearing amalgam vs. composite restorations; trends to *improved* scores among subjects with amalgam fillings [146, 147]
- No consistent evidence linking prenatal mercury exposure from dental amalgam to mental / psychomotor development and neurobehavioral consequences based on the Seychelles Child Development Study among inhabitants with traditionally high fish consumption [148-150]:
  - No meaningful adverse associations between prenatal exposure to maternal amalgam (with or without adjustment for pre/post-natal methylmercury exposure) and any tested outcomes (66 months)
  - 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
  - No associations between maternal amalgam surfaces and Bayley Scales of Infant Development-II (9 and 30 months)
  - No associations between amalgam status during pregnancy and cognitive, language and perceptual functions, and scholastic achievement (at 5 years)
- Per 7-year follow up, no consequential differences except statistically non-significant changes in tremor and some other neurological signs among children treated with amalgam vs. resin-based composites [151]

Similarities between Overall Metal Reactivity and Dental Amalgam Related Responses

- Possible increases of metal levels in biofluids
- Similar new *vs*. old mechanistic concepts:
  - Metal release attributed to amalgam corrosion rather than electrochemical reactions due to metals with different electric potentials [100]
- Role of hypersensitivity [105-107]:
  - OLL – Oral Lichenoid Lesions may represent true delayed (type IV) hypersensitivity with a trans-epithelial route of entrance of metal haptens released from dental amalgam
  - In addition to the oral mucosa related lesions, dental amalgam may elicit skin sensitivity manifesting as allergic dermatitis
- Amalgam tattoos bearing histopathological evidence of FBR – Foreign Body Response:
  - Inflammatory reactions and tissue responses such as foreign body granuloma with multinucleated giant cells [97]

Individual Susceptibility to Mercury Toxicity

as a Sum-effect of Different Modifying Factors in Health Outcomes Attributable to Dental Amalgam

Putative Effect Modifiers of Amalgam-Related Mercury Toxicity

- **Genetic markers** related to mercury kinetics and toxicity, or neurobehavioral functions:
  - SNPs in glutathione-related genes, selenoproteins, and metallothioneins
  - MT1M_rs2270837 and MT2A_rs10636 as modifiers in occupational / non-occupational exposure
  - Casa Pia Dental Amalgam Clinical Trial in children [175-178]:
    - Sex-codependent modification of mercury-attributed neurobehavioral effects by SNPs in coproporphyrinogen oxidase CPOX4, catechol-O-methyltransferase COMT, and metallothioneins
    - CPOX4_rs1131857 as a SNP with the broadest range of attributed effects
- **Sex/age**:
  - Longer mercury retention in kidneys and therefore lower elimination rates in women vs. men [21]
  - Younger populations experiencing more adverse effects; girls having higher urinary mercury [44]
  - Blood mercury levels similar for men and women <40 years, but higher among older women [29]
  - Higher urinary mercury levels in women vs. men, with the difference increasing with age [30, 37]
  - A slightly higher risk trend for Alzheimer's disease among women vs. men [40]
  - More frequent patch test positivity to amalgam among women [111]
  - Combined role of sex and BMI is higher in men vs. women [24]
  - Various sex-dependent risk trends for being small for gestational age [154] and other neurodevelopmental outcomes [149, 175-178]

- **Country/residence area**: various factors related to geographic location, race/ethnicity, genetic background, diet, socioeconomic status, religious and cultural traditions, *etc*.
- **Miscellaneous**: equivocal evidence on putative effects from CT, MRI, cell phones

Hg^0?

MeHg?

Urine Mercury for Dental Amalgam Exposure and Hair Mercury for Dietary Exposure, *Or Not So Simple?*

Recent Evidence Challenging the Accuracy of Postulated Exposure Indicators

Urine Mercury May Overestimate Exposure from Dental Amalgam

[182, *Sherman et al 2013*]

Environmental Science & Technology

Article

pubs.acs.org/est

New Insight into Biomarkers of Human Mercury Exposure Using Naturally Occurring Mercury Stable Isotopes

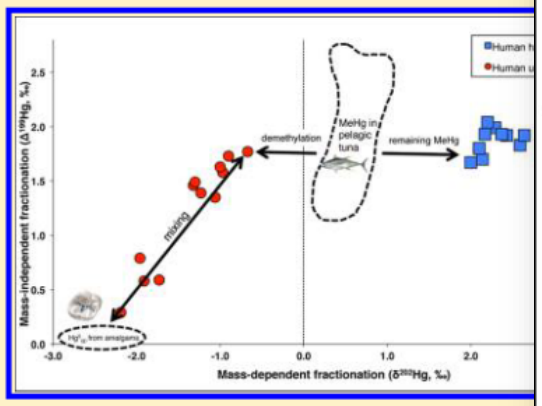
Laura S. Sherman,[†,*] Joel D. Blum,[†] Alfred Franzblau,[‡] and Niladri Basu[‡]

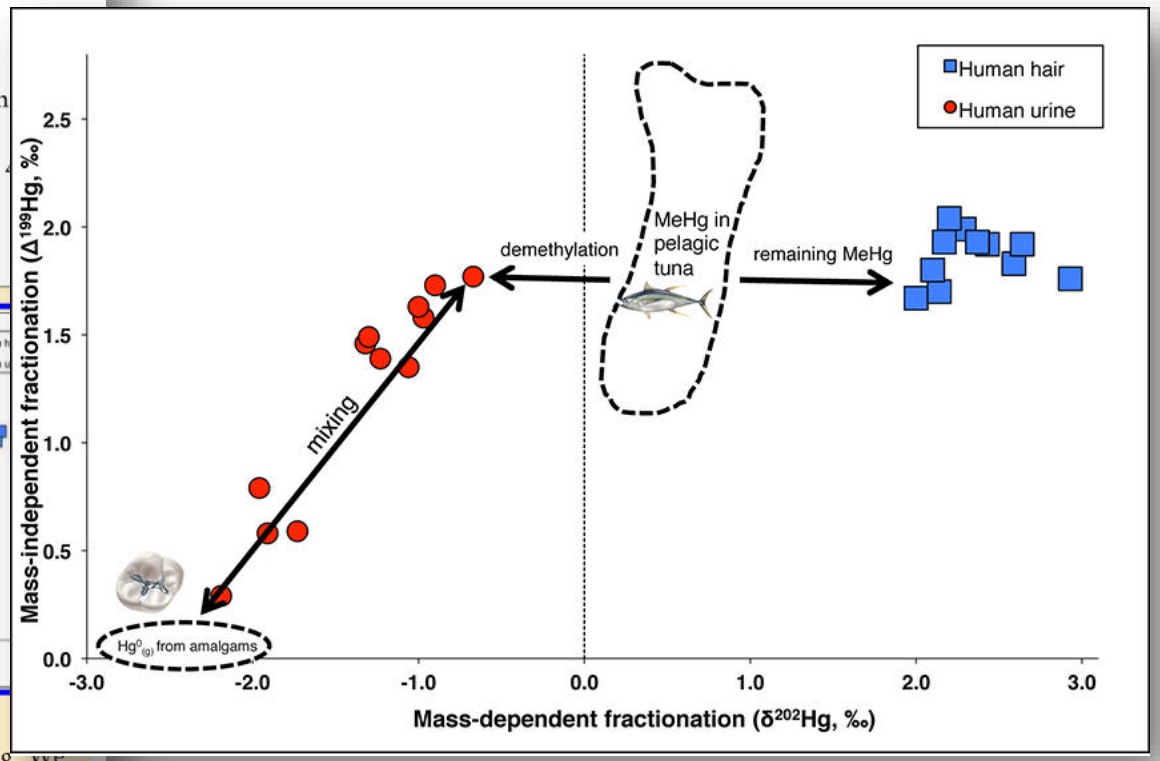
[†]Department of Earth and Environmental Sciences, University of Michigan, 1100 N. University Ave., Ann Arbor, Michigan United States

[‡]Department of Environmental Health Sciences, University of Michigan, 1415 Washington Heights, Ann Arbor, Michigan United States

Supporting Information

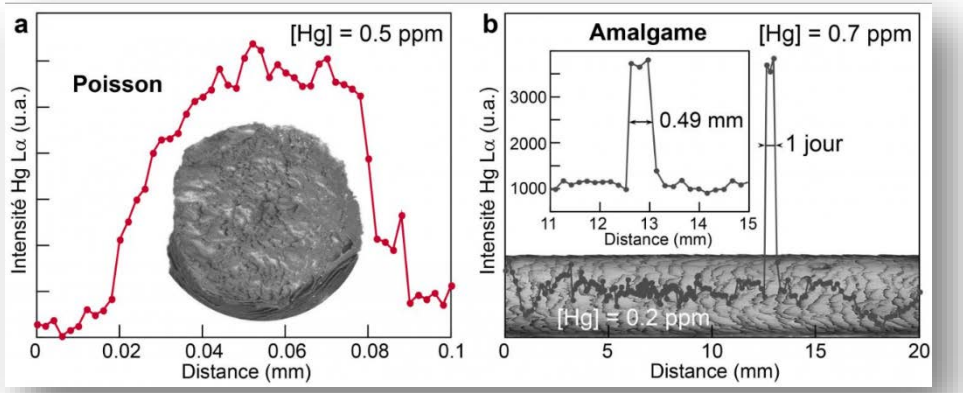
ABSTRACT: Human exposure to methylmercury (MeHg) and elemental mercury vapor ($Hg^0_{(g)}$) are often estimated using total Hg concentrations in hair and urine, respectively. We investigated whether Hg stable isotopes could be used to better distinguish between exposure to $Hg^0_{(g)}$ versus MeHg. We found that hair from North American dental professionals was characterized by high positive Δ^{199}Hg values (mean = 1.86‰, 1 SD = 0.12‰, n = 11). This confirms that among people who regularly consume fish, total Hg concentrations in hair reflect exposure to MeHg. In contrast, we found that urine from the same individuals was characterized by a range of Δ^{199}Hg values (0.29 to 1.77‰, 2 SD = 0.06‰, n = 12) that were significantly correlated to the number of dental amalgams in each individual's mouth. We hypothesize that fish-derived MeHg is demethylated within the body, causing mass-dependent fractionation and the excretion of inorganic Hg in urine. Mercury in urine therefore represents a mixture of demethylated fish-derived MeHg and amalgam-derived inorganic Hg. We estimate that the majority (>70%) of Hg in urine from individuals with <10 dental amalgams is derived from ingestion of MeHg in fish. These data suggest that within populations that consume fish, urine total Hg concentrations may overestimate Hg exposure from personal dental amalgams.





Hair Mercury May Overestimate Exposure from Fish Consumption

Alain Manceau et al. Chemical Forms of Mercury in Human Hair Reveal Sources of Exposure. *Environmental Science & Technology (2016)* https://phys.org/news/2016-09-tracking-mercury-contamination-human-hair.html



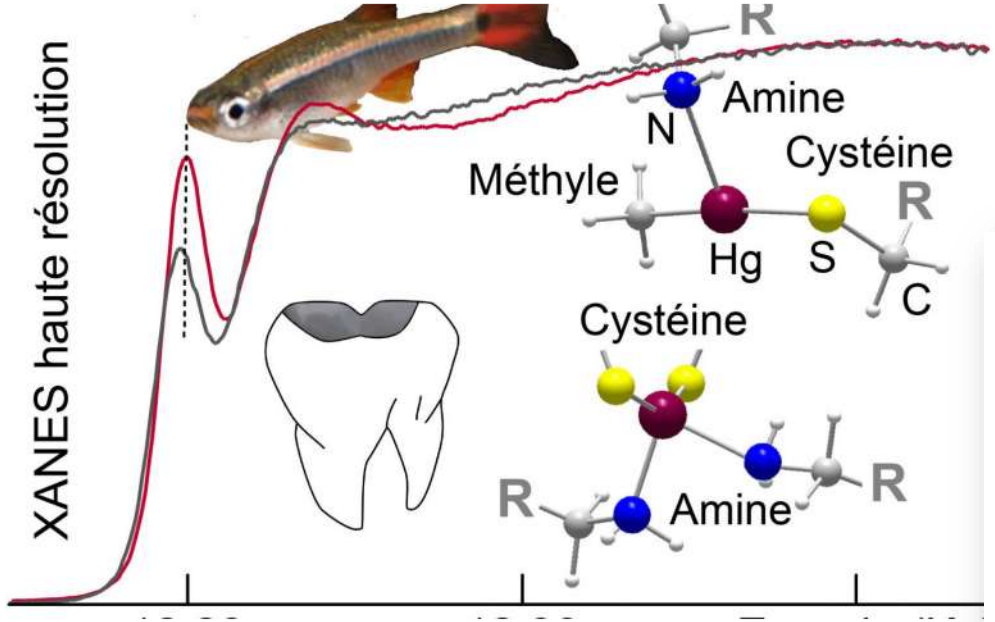
Distribution of Hg in hair.
(a) Transverse profile of Hg in a single strand from a healthy individual.
(b) The mercury spike records the contamination event due to amalgam extraction.

PHYS.ORG Nanotechnology Physics Earth Astronomy & Space Technology Chemistry

Home » Earth » Environment » September 22, 2016

Tracking down the origin of mercury contamination in human hair

September 22, 2016, CNRS



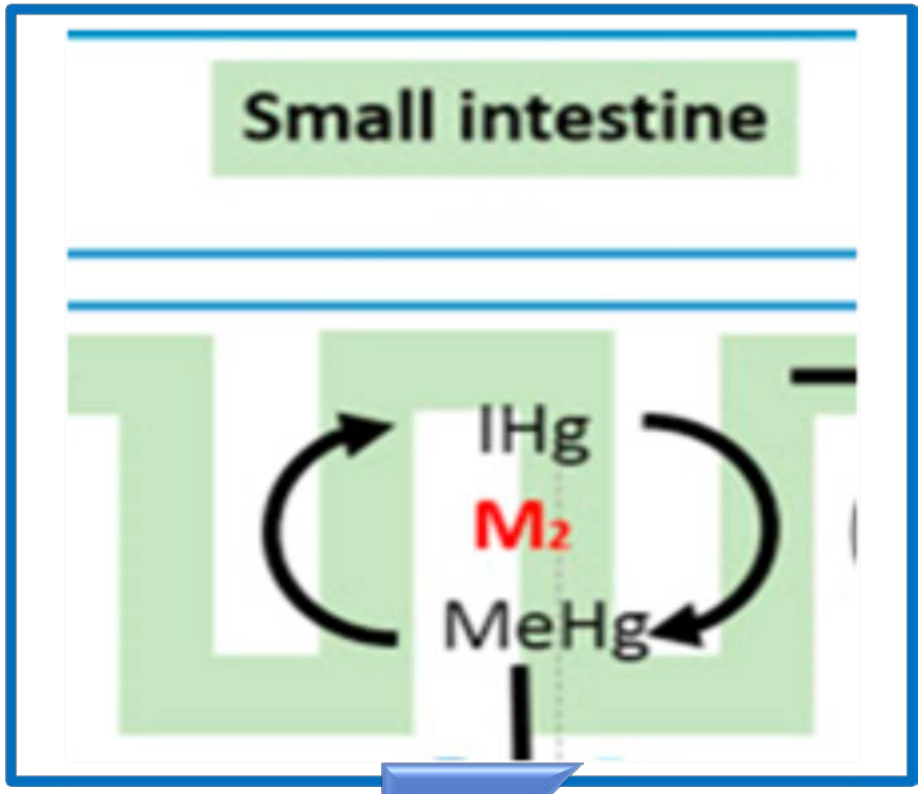
Spectral signature of two chemical forms of mercury in hair, one originating from fish consumption and the other from removal of a der
amalgam. In the first case (fish), mercury is methylated and bonded to one cysteine sulfur and one amine group from hair proteins (mo
keratin). In the second (dental amalgam), mercury is bonded to two cysteine sulfurs and two amine groups from hair proteins. Credit:
A.Manceau

New analytical capabilities to identify chemical forms of mercury in human hair

Until today, depending on the suspected source of contamination, mercury intake has been monitored by measurement of mercury concentration in urine, blood, or scalp hair. These measurements help to diagnose the dose of poisoning and provide data for epidemiological studies, but provide incomplete information on the source of mercury exposure essential for treatment and forensic investigations.

"Although urinary mercury concentration is considered to be the most accurate and widely used biomarker for assessing chronic exposure to mercury vapour and divalent mercury, we showed that inorganic mercury from dental amalgams can be detected in hair with distinct intermolecular structure from that of methylmercury from fish consumption" says Jean-Paul Bourdineaud, Professor of environmental toxicology at the University of Bordeaux, France.

"Epidemiological studies on mercury intake through fish consumption assume that hair concentration is an indicator of only this source. Our results show that this assumption may not always be true" says Kathryn Nagy, Professor of Earth and Environmental Sciences at the University of Illinois at Chicago.



In Vivo Cross-Transformation of Mercury Species:

What Are Health Consequences Attributable to Dental Amalgam *vs*. Diet?

In Vivo Cross-Transformation of Inorganic and Organic Mercury

- Inorganic Hg formation via mercury demethylation
  (Uchikawa et al. Demethylation of methylmercury and the enhanced production of formaldehyde in mouse liver. J Toxicol Sci. 2016)
- Organic MeHg formation via mercury methylation by the gut microbiota in aquatic and terrestrial animals including mammals
  (Li et al. Intestinal Methylation and Demethylation of Mercury. Bull Environ Contam Toxicol. 2018; Martín-Doimeadios et al. Is gastrointestinal microbiota relevant for endogenous mercury methylation in terrestrial animals? Environ Res. 2017)

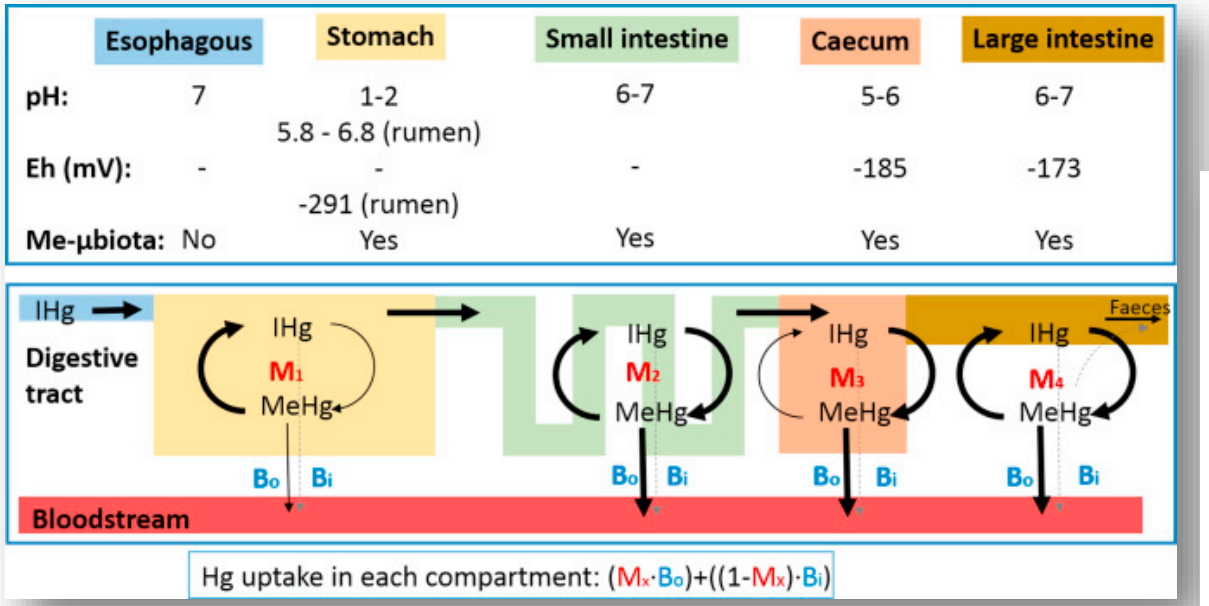


Fig. 1. Scheme representing the potential compartments of Hg transformation in the digestive tract of monogastric and ruminants. Some determinants of the conversion between MeHg and IHg are the pH, the redox potential (Eh) and the presence of microbiota with the capacity to methylate IHg (*i.e.* sulfate-reducing bacteria and others). The overall methylation rate (Mx) should determine the concentration of MeHg in each compartment, and the bioavailability of MeHg through the compartment mucose (Bo) should determine the extraction (absorption) of MeHg from the methylation-demethylation cycle towards the bloodstream. Alternatively, the remaining IHg could be also absorbed with a different bioavailability factor (Bi). The remaining unabsorbed Hg (either in organic or inorganic form) would pass to the next compartment where the process should occur with different values of Mx and, probably of Bo and Bi. pH and Eh values extracted from Broudiscou et al., 2014, Lizardo et al., 2012.

Limitations and Challenges of the Existing Evidence on Dental Amalgam Safety

- Evidence synthesis and generation of actionable knowledge affected by:
  - Certain limitations in individual articles:
    - Insufficient assessment of exposure
    - Poor generalizability to the US general population or US dental professionals
  - **Cross-cutting methodological limitations:**
    - **Lack of appropriate measurement approaches to identifying all possible exposure sources and distinguishing between the impacts of dental amalgam *vs.* other sources**
    - Urine may not be the main excretion pathway
- Risk assessment further complicated by:
  - Interindividual variability and enhanced susceptibility
  - Unaccounted exposure (*e.g.,* dietary and cultural traditions, environmental pollution)
  - *In vivo* cross-transformation of amalgam-derived Hg and dietary MeHg

Instead of Conclusion

- Mercury increase in biofluids as the main *subclinical* outcome attributable to dental amalgam exposure:
  - *Non-occupational*: no new evidence on risks in vulnerable populations
  - *Occupational*: decreasing mercury levels in the US and European countries; however, mercury levels due to occupational *vs*. non-occupational exposure appear to remain higher
- No consistent evidence on whether dental amalgam attributed mercury increases may cause *clinically-manifested* adverse outcomes
- Risk assessment complicated by various factors:
  - Additional exposure sources other than amalgam (*e.g.,* seafood, special products)
  - Effect modification by demographic, genetic, and environmental factors
  - Lack of reliable markers for individual susceptibility
  - ***Lack of reliable mercury measurements for unequivocal causality analysis (i.e., dental amalgam vs. diet and other sources)***

Next Steps:

Turning New Knowledge into More Accurate Causality Assessment and Better Safety

Image adapted from: https://www.transperfect.com/blog/four-reasons-why-translation-quality-measurements-are-important

Recent Advances in Biomonitoring for Mercury Exposure

Alfred Franzblau, MD
University of Michigan School of Public Health
Ann Arbor, Michigan

Financial Interests

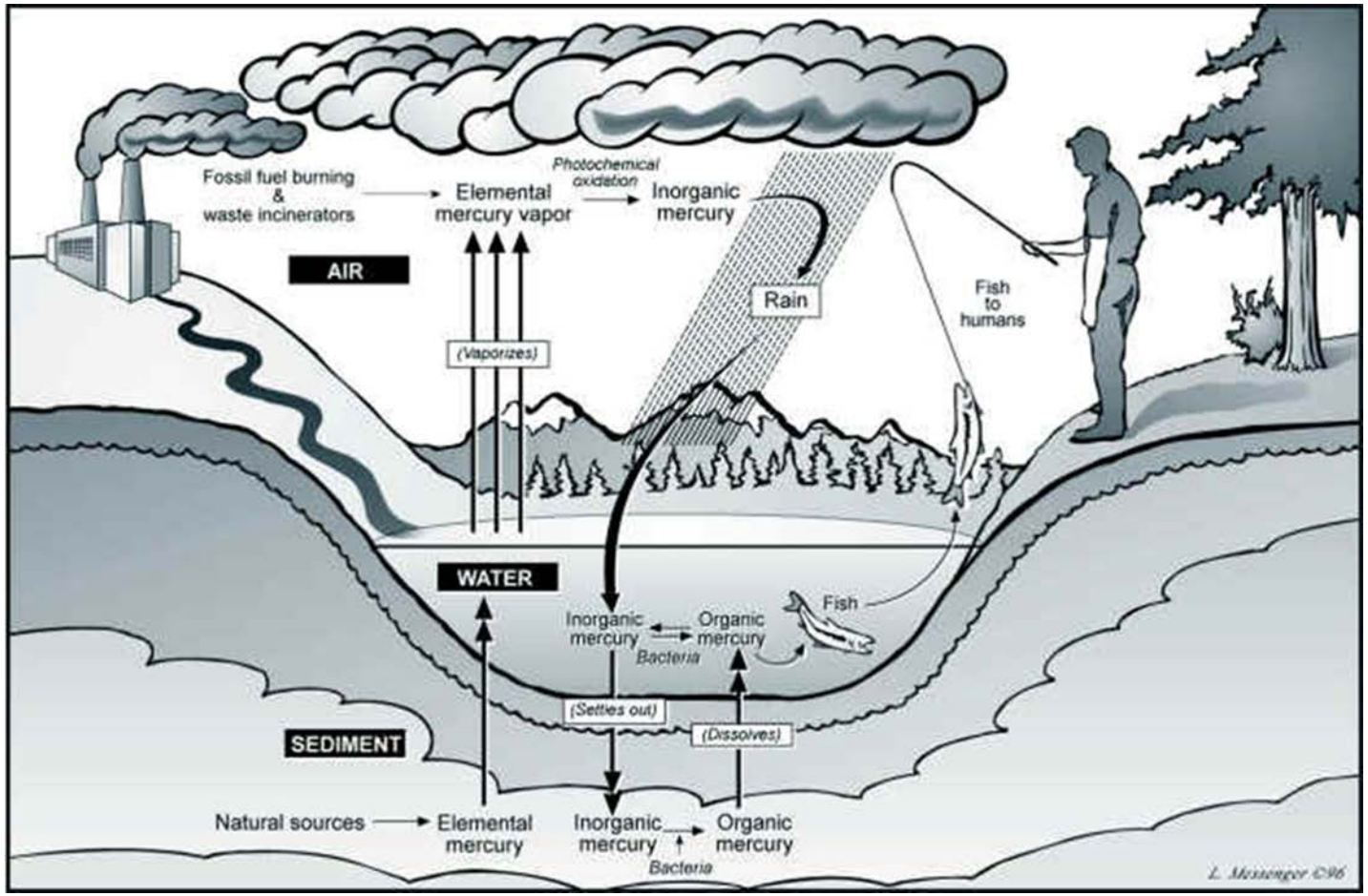
I do not have any financial interests to report in relation to mercury and dental amalgam. However, in past years my colleagues and I published a number of studies that included data collected in cooperation with the American Dental Association (ADA) and/or the Michigan Dental Association (MDA). These studies did not involve any grants or funding from the ADA or MDA, and final editorial control of publications was with University of Michigan investigators.

Primary Questions to be Addressed

- What is an appropriate biomarker of exposure to mercury from dental amalgam, i.e., elemental mercury (Hg^0)?

- What is an appropriate biomarker of exposure to mercury from fish, i.e., methylmercury (MeHg)?

Background: The Mercury Cycle



Background: Exposure & Monitoring

- For most people, after exclusion of occupational exposures (which are mostly related to inhalation of Hg^0 vapor), the primary sources of mercury exposure are:
  - Emissions of elemental mercury (Hg^0) from amalgam tooth fillings
  - Ingestion of methylmercury (MeHg) from fish
- Most mercury in hair is MeHg (>80%), and so studies often have measured total Hg in hair as a biomarker of MeHg exposure from fish.
- Almost all Hg in urine is inorganic Hg (>98%), so measurement of total Hg in urine has often been used as a biomarker of exposure to Hg^0.

Source: Sherman 2013

Background: Methylation/Demethylation

- Measurement of total Hg in urine or hair as biomarkers of exposure to Hg^0 and MeHg, respectively, assumes that there is little or no demethylation or methylation (respectively) in vivo.
- However evidence has accumulated to suggest that these assumptions may not be correct. As summarized in the recent FDA review:
- "… 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." (FDA 2019, page 51)

Evidence of Demethylation: Epidemiology Studies

- Some studies have shown an association between fish consumption and total mercury levels measured in urine, thereby suggesting that demethylation can occur in-vivo, and inorganic Hg derived from demethylation of ingested MeHg can be excreted in urine. (Barregard 2006; Johnsson 2005; Levy 2004; McKelvey 2011, 2018; Snoj Tratnik 2019; Suzuki 1993)
- Other studies have not shown such an association. (Goodrich 2016; Dunn 2008)
- Demethylation of MeHg by intestinal microbes has been demonstrated, but demethylation may also occur in body tissues. (Clarkson 2002; Li 2019; Sherman 2013)

Evidence of Demethylation: Direct Measurement

- By analyzing Hg stable isotopes in hair and urine, one can distinguish between sources of exposure to MeHg versus Hg^0.
- Using analysis of mercury stable isotopes, it has been shown that mercury in urine represents a mixture of demethylated fish-derived MeHg, and amalgam-derived inorganic Hg.
- It is estimated that as much as 70% (or more) of total Hg in urine from individuals with <10 dental amalgams can be derived from ingestion of MeHg in fish among persons who regularly consume fish.
- Within populations that consume fish, measurement of urine total Hg may overestimate Hg exposure from personal dental amalgam.

Source: Sherman 2013

Evidence of Methylation: In-vivo, In-vitro and Genetic Studies

- In-vitro studies have documented methylation of elemental or inorganic Hg by specific human bacterial species, thus suggesting the theoretical possibility of methylation of amalgam-derived mercury in-vivo by human oral and/or gut flora. (Heintze 1983; Martin-Doimeadios 2017; Rowland 1975)
- Persons with amalgam fillings have "higher amounts of both organic and inorganic mercury" in saliva than nonamalgam control groups. This study did not assess Hg in urine or hair. (Leistevuo 2001)
- More recent work has identified a two-gene cluster (*hgcAB*) that is required for mercury methylation by bacteria. (Gilmour 2013; Parks 2013)
- Using the two-gene cluster as a genetic marker, one study found no bacteria from ~1500 human & mammalian microbiomes that encoded these genetic markers for mercury methylation, "suggesting a low risk of endogenous MeHg production". (Podar 2015)
- Another study of 17 pregnant women detected no *hgcA* in stool samples. (Rothenberg 2016)

Evidence of Methylation: Epidemiology Studies

- Some epidemiology studies found a positive correlation between number of amalgam fillings and hair mercury. (Barghi 2012; Diez 2008; Okati 2012)
  - However, one study also found a positive correlation between level of education and frequency of fish consumption, and level of education and number of amalgam fillings. "It could be concluded that higher levels of education leads to more attention to teeth hygiene and consequently a higher number of amalgam fillings." Hence, the association between amalgam fillings and hair mercury could be due to confounding by level of education. (Barghi 2012)
- Some epidemiology studies found no association between amalgam fillings and hair mercury. (Dunn 2008; Goodrich 2016)

Evidence of Methylation: Direct Measurement

- In addition to examining demethylation, Sherman et al (2013) also examined potential methylation of Hg^0 that might contribute to total hair Hg.
- Based on measurement of mercury stable isotopes, "…among people who regularly consume fish, total Hg concentrations in hair reflect exposure to MeHg." There was no evidence of significant in-vivo methylation of Hg^0 contributing to mercury in hair, even among those with >10 fillings. (Sherman 2013)
- However, the study group was small (n=12), all consumed fish, and the mean estimated total mercury intake from fish was high compared to the mean for the entire MDA study population (n=511; 0.403 vs 0.08 ug/kg body wt/day) (Sherman 2013; Goodrich 2011)

Conclusions: Demethylation of Hg

- Within populations that consume fish, measurement of urine total Hg may overestimate Hg exposure from personal dental amalgam due to demethylation of MeHg in-vivo.

Conclusions: Methylation of Hg

- There is evidence that mercury from amalgam can be methylated in-vitro by bacteria. There is evidence that mercury from amalgam can be methylated in-vivo, but the literature is conflicting regarding the magnitude and significance.
- One small study using direct measurement of mercury stable isotopes among above-average fish consumers did not find evidence of methylation of Hg^0 in-vivo, even among those with $\geq$10 amalgam fillings.
- Overall, it is not clear how commonly methylation of Hg occurs in-vivo, but if it occurs at all, the impact on measurement of total mercury in hair appears to be small.

Final Thoughts

- Analyses of mercury stable isotopes, as demonstrated in Sherman (2013) and others, is an important research tool, but not a practical method for epidemiological studies or the clinical setting at this time.
  - Expensive and time consuming
  - At present, few institutions in the US have the technical capacity
  - Requires detailed knowledge of volume and type of fish consumption for results to be properly interpretable
- At present, in terms of biomarkers for population studies, I would recommend measuring Hg in hair and urine, but also assessing exposure to fish and amalgam (via questionnaires and/or examination), and possibly making statistical adjustments in models.
- It would be helpful to have a larger study using direct measurement of mercury stable isotopes to look at a wider range of subjects with regard to both fish consumption and number of amalgam fillings.

References

- Barghi M, Behrooz RD, Esmaili-Sari A, Ghasempouri SM. Mercury exposure assessment in Iranian pregnant women's hair with respect to diet, amalgam fillings, and lactation. Biol Trace Elem Res. 2012;148:292-301.
- Barregard L, Horvat M, Mazzolai B, et al. Urinary mercury in people living near point sources of mercury emissions. Sci Tot Environ. 2006;368:326-334.
- Clarkson TW. The three modern faces of mercury. Environ Hlth Persp. 2002;110(Suppl 1):11-23.
- Diez S, Montuori P, Pagano A, et al. Hair mercury levels in an urban population from southern Italy: Fish consumption as a determinant of exposure. Environ Internat. 2008;34:162-167.
- Dunn JE, Trachtenberg FL, Barregard L, Bellinger D, McKinlay S. Scalp hair and urine mercury content of children in the Northeast United States: The New England Children's Amalgam Trial. Environ Res. 2008;107:79-88.
- FDA [US Food and Drug Administration]. Epidemiological evidence on the adverse health effects reported in relation to mercury from dental amalgam: Systemic literature review (2010-Present). September 2019.
- Gilmour CC, Podar M, Bullock AL, et al. Mercury methylation by novel microorganisms from new environments. Environ Sci Tech. 2013;47:11810-11820.

References

- Goodrich JM, Chou H-N, Gruninger SE, Franzblau A, Basu N. Exposures of dental professionals to elemental mercury and methylmercury. J Exp Sci Environ Epid. 2016;26:78-85.
- Heintz U, Edwardsson S, Derand T, Birkhed D. Methylation of mercury from dental amalgam and mercuric chloride by oral streptococci in vitro. Scand J Dent Res. 1983;91:150-152.
- Johnsson C, Schutz A, Sallsten G. Impact of consumption of freshwater fish on mercury levels in hair, blood, urine, and alveolar air. J Tox Environ Hlth. 2005;68(2):129-140.
- Laffont L, Sonke JE, Maurice L, et al. Anomalous mercury isotopic compositions of fish and human hair in the Bolivian Amazon. Environ Sci Technol. 2009;43:8985-8990.
- Laffont L, Sonke JE, Maurice L, et al. Hg speciation and stable isotope signatures in human hair as a tracer for dietary and occupational exposure to mercury. Environ Sci Tech. 2011;45:9910-9916.
- Leistevuo J, Leistevuo T, Helenius H, et al. Dental amalgam fillings and the amount of organic mercury in human saliva. Caries Res. 2001;35:163-166.
- Levy M, Schwartz S, Dijak M, et al. Childhood urine mercury excretion: dental amalgam and fish consumption as exposure factors. Environ Res. 2004;94:283-290.

References

- Li H, Lin X, Zhao J, et al. Intestinal methylation and demethylation of mercury. Bull Environ Contam Toxicol. 2019;102:597-604.
- Martin-Doimeadios RCR, Mateo R, Jimenez-Moreno M. Is gastrointestinal microbiota relevant for endogenous mercury methylation in terrestrial animals? Environ Res. 2017;152:454-461.
- McKelvey W, Jeffery N, Clark N, Kass D, Parsons PJ. Population-based inorganic mercury biomonitoring and the identification of skin care products as a source of exposure in New York City. Environ Hlth Perspec. 2011;119(2):203-209.
- McKelvey W, Alex B, Chernov C, et al. Tracking declines in mercury exposure in the New York City adult population, 2004-2014. J Urban Hlth. 2018;95:813-825.
- Okati N, Sari AE, Ghasempouri SM. Hair mercury concentrations of lactating mothers and breastfed infants in Iran (Fish consumption and mercury exposure). Biol Trace Elem Res. 2012;149:155-162.
- Parks JM, Johs A, Podar M, et al. The genetic basis for bacterial mercury methylation. Science. 2013;339(6125):1332-1335.

References

- Podar M, Gilmour CC, Brandt CC, et al. Global prevalence and distribution of genes and microorganisms involved in mercury methylation.
- Rothenberg SE, Keiser S, Ajami NJ, et al. The role of gut microbiota in fetal methylmercury exposure: Insights from a pilot study. Toxicol Letters. 2016;242:60-67.
- Rowland IR, Grasso P, Davies MJ. The methylation of mercuric chloride by human intestinal bacteria. Experientia. 1975;31:1064-1065.
- Sherman LS, Blum JD, Franzblau A, Basu N. New insight into biomarkers of human mercury exposure using naturally occurring mercury stable isotopes. Environ Sci Tech. 2013;47:3403-3409.
- Snoj Tratnik J, Falnoga I, Mazej D, et al. Results of the first national human biomonitoring in Slovenia: Trace elements in men and lactating women, predictors of exposure and reference values. Int J Hyg Environ Hlth. 2019;222:563-582.
- Suzuki T, Hongo T, Abe T, et al. Urinary mercury level in Japanese school children: influence of dental amalgam fillings and fish eating habits. Sci Total Environ. 1993;136:213-227.

U.S. FOOD & DRUG ADMINISTRATION

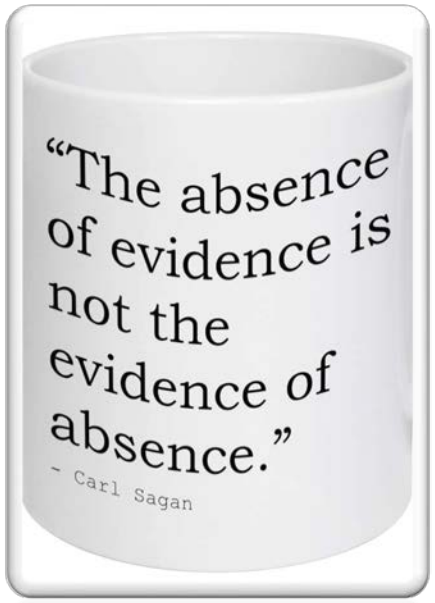
Dental Amalgam:

Summary / Gap Analysis

November 13, 2019: Immunology Devices Panel of the Medical Devices Advisory Committee Meeting

Yelizaveta (Lisa) Torosyan, MD, PhD

Consistency between Current and Previous Findings on Dental Amalgam Safety, BUT…

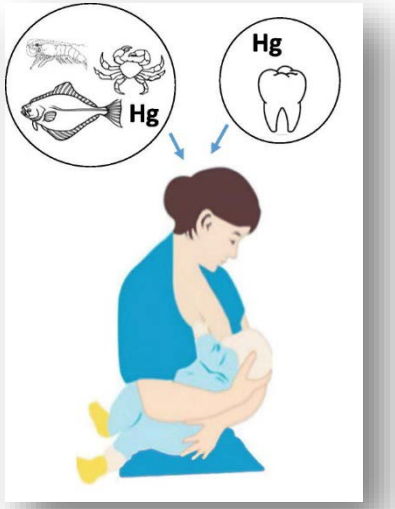


- No new evidence was found suggesting considerable risk increases for the US general population or dental professionals
- However, the current risk considerations are based on **the LACK of strong evidence on amalgam-attributed adverse outcomes, rather than the existing evidence eliminating their possibilities**

Main Knowledge Gaps and Evidence Deficiencies Affecting Comprehensive Evaluation of Dental Amalgam Safety

How to accurately distinguish between the mercury species from two main sources of exposure?

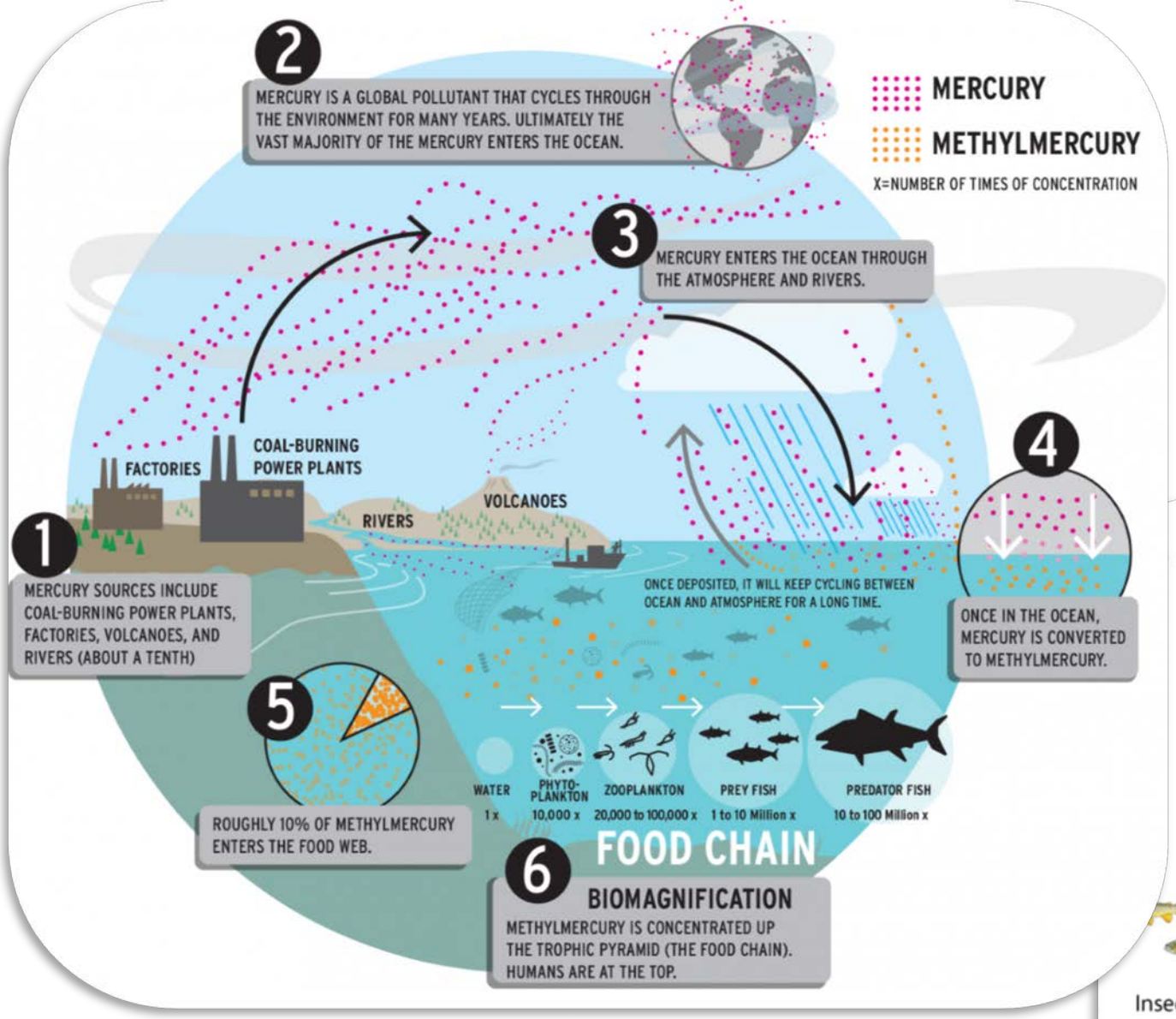
- Existing clinical evidence affected by **the lack of updated mercury measurement methodologies**:
  - The need for evaluating possible health consequences of *in vivo* cross-transformation of mercury species ($Hg^0 \leftrightarrow$ MeHg)
  - Combined assessment of the main mercury exposure sources *(i.e.,* amalgam vs. seafood)
  - Accurate causality analysis of adverse health effects unequivocally attributable to dental amalgam



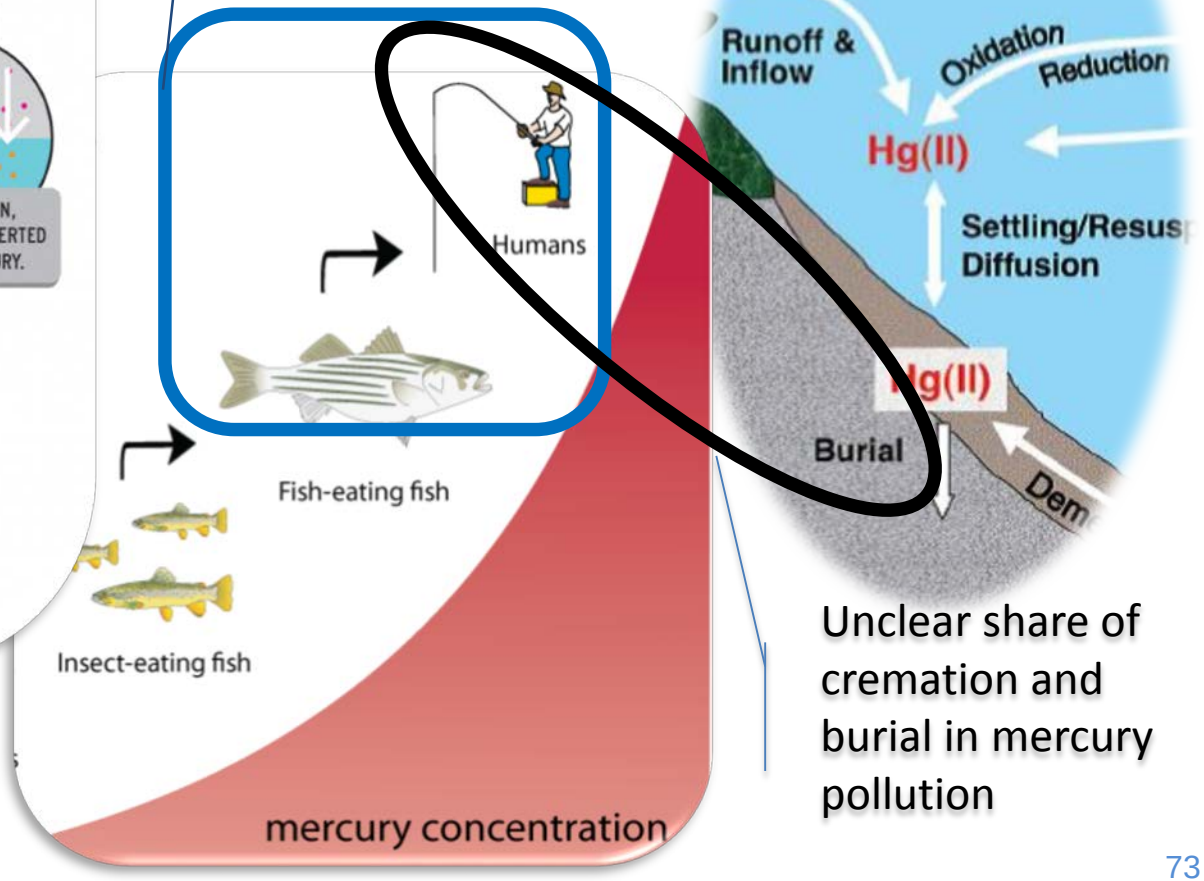
Only 10% of variance in breast milk mercury concentrations was explained by seafood intake alone and 46% together with amalgam fillings (*Vollset et al 2019, Norway; Addendum*). ***What are the causes for the remaining 50% of variance?***

- Dental amalgam-specific risk assessment affected by **the unaccounted exposure sources and modifying effects**:
  - Genetic/non-genetic factors reflecting individual susceptibility to mercury toxicity
  - Additive effects due to unconventional sources of mercury exposure (*e.g.*, mining, folk medicines, special products, ritual practices, *etc.*)

Dental Amalgam & Beyond



Humans at the top of mercury-related food chain



Unclear share of cremation and burial in mercury pollution

Images adapted from: https://www.nps.gov/subjects/air/humanhealth-toxics.htm ; https://www.google.com/url?sa=i&rct=j&q=&esrc=s&source=images&cd=&ved=2ahUKEwi4nf6wuP7kAhVyAWMBHWoYCJsQjRx6BAgBEAQ&url=https://www.harvardmagazine.com/2018/07/elsie-sunderland-harvard&psig=AOvVaw1h7jOiKmvBHcOnAJjIWFpS&ust=1570132734391641 ; http://www.google.com/url?sa=i&rct=j&q=&esrc=s&source=images&cd=&cad=rja&uact=8&ved=2ahUKEwi4nf6wuP7kAhVyAWMBHWoYCJsQjRx6BAgBEAQ&url=/url?sa%3Di%26rct%3Dj%26q%3D%26esrc%3Ds%26source%3Dimages%26cd%3D%26ved%3D2ahUKEwi4nf6wuP7kAhVyAWMBHWoYCJsQjRx6BAgBEAQ%26url%3Dhttps://11and4tht.wordpress.com/2013/11/14/mercury-in-fish-a-pictorial-description-of-the-mercury-cycle-in-lakes/%26psig%3DAOvVaw1h7jOiKmvBHcOnAJjIWFpS%26ust%3D1570132734391641&psig= AOvVaw1h7jOiKmvBHcOnAJjIWFpS&ust=1570132734391641

Minding the Gaps and Prioritizing Next Steps on Dental Amalgam Safety Evaluation

- ✓Addressing the existing knowledge gaps and methodological deficiencies:
  - ✓Evaluation of health consequences of *in vivo* cross-transformation of mercury species
  - ✓Optimized methodology for mercury speciation analysis
  - ✓Unequivocal causality analysis of mercury exposure sources, *e.g.*, amalgam *vs.* diet
  - ✓Evaluation of additive effects from unconventional sources of exposure, *e.g.*, folk medicine
  - ✓Clarified subclinical and clinical spectrums of amalgam-attributable adverse effects
  - ✓Discovery and implementation of markers and predictors of enhanced susceptibility
  - ✓Evaluation of dental amalgam share in mercury-related environmental impact

- ✓**Deriving better quality (pre)clinical evidence for more informed decision making**

Panel Discussion:
Weighing the Evidence