(DRAFT) An overview of the science underlying the mercury dental amalgam controversy

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Summary

Mercury dental amalgam -- used for “silver” fillings -- continuously releases low levels of mercury vapor, which is readily absorbed by the body. Whether these levels are safe or harmful has been a topic of scientific debate. Three recent reanalyses of the Portugal Children’s Amalgam Trial, a randomized, controlled, clinical trial that was once widely cited as evidence of safety, now reveal harm. Other recent findings reveal that at least six genes have common variants that convey increased susceptibility to mercury toxicity. Many more such genes are likely due to the particular toxic mechanism of mercury. The most sensitive target for mercury toxicity is the developing neuron. Cell culture studies show clear effects on nerve growth at mercury concentrations found in neonatal infants of amalgam-bearing mothers. Due to historical circumstances, dental amalgam has never undergone the regulatory proof-of-safety testing that is required for other medical implants. Scientific evidence may support the safety of amalgam for some adults, in limited amounts, for a limited number of years, provided the exposures during placement and removal are ignored. But better alternatives exist, which have lower costs when societal and environmental externalities are considered. Therefore, from a public policy perspective, mercury dental amalgam should be banned. The US Food and Drug Administration (FDA) is actively reviewing the issue but has given no further information since 2010. Several other countries have banned or restricted dental amalgam. Amid the current US regulatory uncertainty, some local governments have passed ordinances aimed at reducing amalgam use.

Highlights

- Dental amalgam is about 50% mercury. It continuously releases mercury vapor, which is readily absorbed by the body (p.12).
- Evidence suggests that a large fraction of amalgam-bearers incur mercury exposures in excess of current environmental health standards (p. 14). Evidence suggests that dentists and dental staff incur mercury exposures in excess of current occupational health standards. Further, it may be impossible to remove an amalgam without violating these standards (p.16).
- A randomized, controlled, seven-year clinical trial, which originally found no association between amalgam and adverse health effects, reveals evidence of harm to children upon reanalysis (p. 22).
- Mercury’s toxic mechanisms are unusually broad (p. 6), yielding a slow onset of a variety of symptoms (p. 9). Toxicity may not be apparent until damage is permanent (p. 7). Current medical textbooks overlook chronic mercury poisoning as a cause of illness (p. 10). Blood and urine mercury levels do not reveal chronic mercury poisoning (p. 11).
- Amalgam has never undergone the regulatory proof-of-safety studies required of other medical implants; it was grandfathered into the regulatory system based on historic use (p. 26). A growing number of countries have banned or restricted amalgam (p. 31).

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Environmental concerns

Mercury is a highly volatile element that does not decompose. Mercury-containing products release toxic mercury throughout their lifecycles, in ways that are often difficult to measure.[1] Dental mercury accounts for about 15% of US mercury end-uses.[2] Environmental concerns regarding mercury from dental amalgam include:

- Mercury bioaccumulates in the food chain and persists in the environment.[3]
- Mercury vapor emissions to air, originating from amalgam, comprise roughly four to five percent, or 4.5 metric tons out of roughly 100 metric tons annually.[4] (Larger sources include combustion, mining, and electronics.) About half of these amalgam emissions are due to human cremation.[5]
- Releases from dental offices are the largest identifiable source of mercury discharged to wastewater treatment plants.[6] Mercury is not removable from wastewater; it is either discharged to the receiving body of water or diverted into biosolids for land application.

Amalgam is more costly than alternatives when external environmental and societal costs are considered, according to a 2012 study by Brussels-based Concorde East/West, an international consulting firm that provides research to the United Nations, the U.S. Environmental Protection Agency, and others.[7]

[1] Cain A, Disch S, Twarski C, Reindl J, Case CR. Substance flow analysis of mercury intentionally used in products in the United States. Journal ofr Industrial Ecology 11(3). 2007. http://oversight.house.gov/wp-content/uploads/2012/01/20100526cain.pdf

[2] USGS (2005): 30 metric tonnes out of 190 metric tonnes total end-use consumption. Kelly TD, Matos GR. USGS. Mercury end-use statistics. Historical statistics for mineral and material commodities in the United States. US Geological Survey. 2005. http://minerals.usgs.gov/ds/2005/140/mercury-use.pdf

[3] Berlin M, Zalups RK, Fowler BA. Mercury. In: Nordberg G, Fowler RA, Nordberg M, Friberg LT, eds. Handbook on the toxicology of metals. 3rd ed. Amsterdam, Boston: Academic Press; 2007.

[4] Cain A. Estimating mercury releases resulting from use of dental amalgam. Testimony before the domestic policy subcommittee of the oversight and governmental reform committee. May 26, 2010

[5] *Ibid.*

[6] National Association of Clean Water Agencies. Mercury source control and pollution prevention program evaluation - Final report. 2002. http://www.nacwa.org/index.php?option=com_content&view=article&id=366%3Amercury-source-control-and-pollution-prevention-program-evaluation-final-report&catid=10%3Awater-quality&Itemid=2

[7] Concorde East-West. The real cost of dental mercury. March 2012.

Health concerns

Dental amalgam contributes significantly to mercury body burden in humans who have amalgam fillings,[8,9] and is the overwhelmingly dominant source of mercury in the central nervous system of the general population.[10] Whether these levels contribute to adverse health effects has long been under debate, but recent studies -- including a reanalysis of the Portugal Children's Amalgam Study once cited as evidence for the safety of amalgam -- now clearly reveal harm.

Toxicity

Chronic mercury toxicity has an insidious onset of nonspecific symptoms that are difficult to diagnose. By the time symptoms are apparent, damage may be permanent. Damage appears to depend on genetic susceptibilities that are just beginning to be identified.

Broad toxic mechanisms

Mercury causes general oxidative damage, equivalent to premature cellular aging, yielding, for example, lipid peroxidation of cell membranes.[11] In addition, mercury binds sulfur, which is ubiquitous in the body -- in membrane transport proteins, in signaling and receptor proteins, in structural proteins, and most importantly, in enzymes, which are needed to facilitate nearly every biochemical process in the body.[12] Also, mercury binds irreversibly to selenium, which is a cofactor in several key enzymes.[13]

At the cellular level, these mechanisms mean that many key processes like membrane functions and enzyme reactions are altered. According to the testimony of metallobiologist Anne Summers at the 2010 FDA hearing on amalgam, "[M]ercury may be involved in many, many diseases.... There's almost no important system in the cell that is not hit by mercury."[14]

Impaired detoxification

In a vicious cycle, mercury blocks detoxification enzymes and their mineral cofactors, thus causing increased retention of many toxicants including mercury itself.[15] For example, mercury oxidizes the glutathione and alters the enzymes that synthesize and recycle this molecule.[16]

Retention toxicity

Once absorbed into certain tissues, mercury is difficult to remove, especially from the central nervous system.[17] Individuals with a reduced ability to excrete mercury may develop retention toxicity, especially after many years.[18] Even within the general population, evidence suggests that mercury accumulates in the body as a function of age and time.[19]

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[8] Risher JF. Elemental mercury and inorganic mercury compounds: Human health aspects. World Health Organization: Geneva: 2003, p 4.

[9] Weiner JA, Nylander. Aspects on health risks of mercury from dental amalgams. In: Chang LW, ed. Toxicology of metals. Boca Raton: Lewis Publishers; 1996.

[10] Berlin 2007, *op cit.*

[11] *Ibid.*

[12] *Ibid.*

[13] *Ibid.*

[14] US Food and Drug Administration, December 14, 2010: Meeting Transcript, 2010 Meeting Materials of the Dental Products Panel, FDA Generated, Gaithersburg, MD, December 14-15, 2010, p 78. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/DentalProductsPanel/UCM242357.pdf

[15] Quig D. Cysteine metabolism and metal toxicity. Altern Med Rev. 1998;3(4):262–270. http://www.ncbi.nlm.nih.gov/pubmed/9727078

[16] *Ibid.*

[17] Mutter J. Is dental amalgam safe for humans? The opinion of the scientific committee of the European Commission. J Occup Med Toxicol. 2011;6(1):2. http://www.ncbi.nlm.nih.gov/pubmed?term=21232090

[18] Mutter J, Naumann J, Guethlin C. Comments on the article "the toxicology of mercury and its chemical compounds" by Clarkson and Magos (2006). Crit. Rev. Toxicol. 2007;37(6):537–549; discussion 551–552. http://www.ncbi.nlm.nih.gov/pubmed?term=17661216

[19] Laks DR. Assessment of chronic mercury exposure within the U.S. population, National Health and Nutrition Examination Survey, 1999–2006. Biometals.

Redistribution toxicity

Natural products including the herb cilantro and the nutritional supplement alpha lipoic acid are dithiols, which mobilize certain metals including mercury. These products are lipophilic, this they tend to equilibrate mercury throughout the body, which effectively means they can redistribute mercury from the dental amalgams into the brain.

Damage may be permanent

Chronic mercury poisoning has no known treatment. The prognosis varies, with some patients appearing to recover fully after cessation of exposure, and others experiencing serious long-term sequelae.[20] A small number of medically-accepted chelating agents may clear the bloodstream and the extracellular spaces but are unlikely to penetrate cell membranes to clear intracellular mercury.[21]

Developmental toxicity

The developing central nervous systems of fetuses and children are particularly vulnerable to mercury.[22] According to Chang's *Toxicology of Metals* (1996), "Available data indicate that mercury from amalgam fillings is transported to the fetus. Animal data show an effect on the anatomical and functional development of the nervous system."[23]

According to Nordberg's *Handbook on the Toxicology of Metals* (2007), "Clear effects on nerve growth arise at the concentration level ... found in neonatal infants of amalgam-bearing mothers."[24]

According to the Agency for Toxic Substances and Disease Registry, "Metallic mercury vapor easily penetrates the placental barrier and accumulates in fetal tissues";[25] and "The results of a regression analysis for mercury in hair, blood, and milk indicated that there was an efficient transfer of inorganic mercury from blood to breast milk and that mercury from amalgam fillings was probably the main source of mercury in breast milk..."[26]

2009;22(6):1103–1114. http://www.ncbi.nlm.nih.gov/pubmed/19697139

[20] Berlin 2007, *op cit.*

[21] Andersen O. Chemical and biological considerations in the treatment of metal intoxications by chelating agents. Mini Rev Med Chem. 2004;4(1):11–21. http://www.ingentaconnect.com/content/ben/mrmc/2004/00000004/00000001/art00003

[22] Counter SA, Buchanan LH. Mercury exposure in children: a review. Toxicol. Appl. Pharmacol. 2004;198(2):209–230. http://www.ncbi.nlm.nih.gov/pubmed/15236954

[23] Weiner 1996, *op. cit.*

[24] Berlin 2007, *op cit,* .citing the following:

Abdulla EM, Calaminici M, Campbell IC. Comparison of neurite outgrowth with neurofilament protein subunit levels in neuroblastoma cells following mercuric oxide exposure. Clin. Exp. Pharmacol. Physiol. [Internet]. 1995 May [cited 2012 Sep 8];22(5):362–3. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7554430

Monnet-Tschudi F, Zurich MG, Honegger P. Comparison of the developmental effects of two mercury compounds on glial cells and neurons in aggregate cultures of rat telencephalon. Brain Res. 1996 Nov 25;741(1-2):52–9. This study of cultured brain cells found that less differentiated cells were more susceptible than well-differentiated cells, and microglial cells were the most sensitive cell type, with effects as low as 10^{-10} M. Astrocytes also showed effects at low levels: 10^{-9} M in immature cultures and 10^{-8} M in mature cultures.

Söderström S, Fredriksson A, Dencker L, Ebendal T. The effect of mercury vapour on cholinergic neurons in the fetal brain: studies on the expression of nerve growth factor and its low- and high-affinity receptors. Brain Res. Dev. Brain Res. [Internet]. 1995 Mar 16 [cited 2012 Sep 8];85(1):96–108. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7781173. Pregnant rats were exposed to two different levels of mercury vapor, yielding neonatal brain concentrations of 4 ng/g and 11 ng/g. At the higher level, many significant changes in NGF (neural growth factor) and associated enzymes, receptors, and mRNA were observed. Even at the lower level, some significant changes were observed.

Drasch G, Schupp I, Höfl H, Reinke R, Roider G. Mercury burden of human fetal and infant tissues. Eur. J. Pediatr. 1994 Aug;153(8):607–10, Fig 3. This autopsy study of the association between maternal amalgams and fetus/infant/child mercury concentrations in lever, kidney, and brain reports brain levels ranging from 0.6 to 23 ng/g, with most between 1 and 10 ng.g. These children had no known mercury exposures aside from maternal amalgams.

Lutz E, Lind B, Herin P, Krakau I, Bui TH, Vahter M. Concentrations of mercury, cadmium and lead in brain and kidney of second trimester fetuses and infants. J Trace Elem Med Biol. 1996 Jun;10(2):61–7.

[25] ATSDR. Toxicological Profile for mercury. 1999, p 174, 175. http://www.atsdr.cdc.gov/toxprofiles/tp46.pdf

[26] *Ibid*., citing Oskarsson A, Schütz A, Skerfving S, et al. Total and Inorganic Mercury in Breast Milk and Blood in Relation to Fish Consumption and Amalgam Fillings in Lactating Women. Archives of Environmental Health: An International Journal. 1996;51(3):234–241.

Synergistic toxicities

Lead

Synergistic toxicities are not addressed under current regulation. Yet a rodent study indicates that mercury and lead are highly synergistic -- the lethal dose of mercury for 1% of the lab rodents ($LD\text{-}1_{Hg}$), combined with the lethal dose of lead for 1% of the rodents (($LD\text{-}1_{Pb}$), killed 100% of the test animals.[27]

Genetic susceptibilities

The emerging science on genetic susceptibilities can explain the otherwise conflicting results within the mercury science literature. Several genes have variants that are associated with poor heavy-metal detoxification, yielding susceptibility to mercury poisoning.

CPOX

Coproporphyrinogen oxidase (CPOX) is an enzyme on the heme synthesis pathway that is needed to make hemoglobin and cytochromes, the latter of which is a class of detoxification enzymes.[28] The CPOX4 variant is associated with both increased sensitivity to the neurobehavioral effects of mercury and increased levels of the urinary porphyrins biomarkers for mercury toxicity.[29,30] The population frequency of the variant is 28%.[31]

BDNF

Brain-derived neurotropic factor (BDNF) is a protein regulator of striatal neuron survival, needed for neuroplasticity, learning, and memory, as well as neuron differentiation.[32,33] The Val6Met variant is believed to suppress secretion of the BDNF protein. This variant is associated with nervous system deficits similar to those observed in chronic exposure to mercury.[34] In a 2005 study, the frequency of this variant, including both the heterozygous and homozygous versions, was 31% for 194 male dentists and 34% for 233 female dental assistants.[35]

5-HTT

5-HTT is a serotonin transporter protein.[36,37] The 5-HTTLPR variant is reported to affect mood and behavior. A 2008 study found significant and consistent associations between increased symptoms and the homozygous variant.[38] A 2010 study found additive effects in certain measures of mood and behavior that were associated with urinary mercury levels.[39]

In the 2010 study, the population frequency of this variant, for the heterozygous and homozygous version, were 40% and 20%, respectively, for males, and 56% and 24% for females.

COMT

Catechol O-methyltransferase (COMT) is a regulatory enzyme that degrades catecholamines, including dopamine, epinephrine, and norepinephrine.[40] The homozygous variant Val158Met was associated with symptoms and mood parameters known to be affected by mercury; and the wild-

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http://www.ncbi.nlm.nih.gov/pubmed?term=PMID%3A%20868 87245

[27] Schubert J, Riley EJ, Tyler SA. Combined effects in toxicology--a rapid systematic testing procedure: cadmium, mercury, and lead. J Toxicol Environ Health. 1978;4(5-6):763–776. http://www.ncbi.nlm.nih.gov/pubmed/731728

[28] Heyer NJ, Bittner AC Jr, Echeverria D, Woods JS. A cascade analysis of the interaction of mercury and coproporphyrinogen oxidase (CPOX) polymorphism on the heme biosynthetic pathway and porphyrin production. Toxicol. Lett. 2006;161(2):159–166. http://www.ncbi.nlm.nih.gov/pubmed/16214298

[29] Woods JS, Heyer NJ, Echeverria D, et al. Modification of neurobehavioral effects of mercury by a genetic polymorphism of coproporphyrinogen oxidase in children. Neurotoxicol Teratol. 2012;34(5):513–521. http://www.ncbi.nlm.nih.gov/pubmed/15580166

[30] Echeverria D, Woods JS, Heyer NJ, et al. The association between a genetic polymorphism of coproporphyrinogen oxidase, dental mercury exposure and neurobehavioral response in humans. Neurotoxicol Teratol. 2006;28(1):39–48. http://www.ncbi.nlm.nih.gov/pubmed/15580166

[31] Echeverria D, Woods JS, Heyer NJ, et al. The association between serotonin transporter gene promotor polymorphism (5-HTTLPR) and elemental mercury exposure on mood and behavior in humans. J. Toxicol. Environ. Health Part A. 2010;73(15):1003–1020. http://www.ncbi.nlm.nih.gov/pubmed/20526950

[32] Echeverria D, Woods JS, Heyer NJ, Rohlman DS, Farin FM, Bittner AC Jr, Li T, Garabedian C. Chronic low-level mercury exposure, BDNF polymorphism, and associations with cognitive and motor function. Neurotoxicol Teratol. 2005 Nov-Dec;27(6):781-96. http://www.ncbi.nlm.nih.gov/pubmed/16301096

[33] Heyer NJ, Echeverria D, Bittner AC Jr, et al. Chronic low-level mercury exposure, BDNF polymorphism, and associations with self-reported symptoms and mood. Toxicol. Sci. 2004;81(2):354–363. http://www.ncbi.nlm.nih.gov/pubmed/15254338

[34] *Ibid.*

[35] Echeverria 2005, *op. cit.*

[36] Echeverria 2010, *op cit.*

[37] Heyer NJ, Echeverria D, Farin FM, Woods JS. The association between serotonin transporter gene promoter polymorphism (5-HTTLPR), self-reported symptoms, and dental mercury exposure. J. Toxicol. Environ. Health Part A. 2008;71(19):1318–1326. http://www.ncbi.nlm.nih.gov/pubmed/18686203

[38] *Ibid.*

[39] Echeverria 2010, *op cit.*

[40] Heyer NJ, Echeverria D, Martin MD, Farin FM, Woods JS. Catechol O-methyltransferase (COMT) VAL158MET functional polymorphism, dental mercury exposure, and self-reported symptoms and mood. J. Toxicol. Environ. Health Part A. 2009;72(9):599–609. http://www.ncbi.nlm.nih.gov/pubmed/19296409

type gene appears to offer some protection against mercury.[41]

Apo

Apolipoprotein appears to play a role in removing heavy metals from the central nervous system.[42,43,44] The ApoE4 allele, which has the fewest sulfur groups, is associated with increased risk for Alzheimer's, while the ApoE2 allele, which has the most sulfur groups, appears protective.[45]

GCL

Glutamyl-cysteine ligase (GCL) is an enzyme that mediates synthesis of glutathione, the main elimination vehicle for mercury.[46] In a 2005 study of gold miners, the GCLM-588T allele was associated with increased mercury levels in blood, plasma, and urine.[47]

Dozens to hundreds more genetic variants may exist, since mercury attacks proteins, which are coded by genes that vary among individuals. According to Nordberg's *Handbook on the Toxicology of Metals* (2007):[48]

> *[M]ercury is a potent cell toxin that affects basic functions of the cell ... this leaves ample scope for genetic polymorphism to manifest itself in varying sensitivity and types of reaction to mercury exposure.*

and,

> *The existence of cases with genetically determined high sensitivity to mercury and with an incidence [of less than one in one hundred exposed]* ***is very likely and is a problem relevant to mercury vapor exposure from dental amalgam in the population****. (Emphasis added.)*

Symptoms -- myriad, variable, and nonspecific

Due to the broad toxic mechanisms, chronic mercury poisoning exhibits an astonishing variety of signs and symptoms.[49] These depend not only on exposure history but on genetic susceptibilities and on nutritional status.[50,51,52]

A 1977 review of clinical symptoms asserts that chronic mercury poisoning is often misdiagnosed due to its insidious onset of vague symptoms and to the unfamiliarity of the disease to members of the health profession.[53] "The induced disease does not appear as a typical entity but as a wide spectrum of clinical pictures."[54] In addition, early-stage chronic mercury poisoning is marked by periods of nonspecific symptoms, alternating with symptomless periods.[55]

Symptoms may include:[56,57,58,59]

- Neurotoxic: fine muscle tremors (beginning with intermittent digital tremors of the extended hand, eventually leading to deterioration of fine motor skills, *e.g.,* illegible handwriting and poor articulation of speech); hypersensitivity to sensory

[41] *Ibid.*

[42] Mutter 2011, *op. cit.*

[43] Mutter 2010, *op. cit.*

[44] Mutter J, Naumann J, Sadaghiani C, Schneider R, Walach H. Alzheimer disease: mercury as pathogenetic factor and apolipoprotein E as a moderator. Neuro Endocrinol. Lett. 2004;25(5):331–339. http://www.ncbi.nlm.nih.gov/pubmed/15580166

[45]

[46] Custodio HM, Harari R, Gerhardsson L, Skerfving S, Broberg K. Genetic influences on the retention of inorganic mercury. Arch Environ Occup Health. 2005;60(1):17–23. http://www.ncbi.nlm.nih.gov/pubmed?term=16961004

[47] *Ibid.*

[48] Berlin 2007, *op. cit.*

[49] Gerstner HB, Huff JE. Clinical toxicology of mercury. J Toxicol Environ Health. 1977;2(3):491–526. http://www.ncbi.nlm.nih.gov/pubmed?term=321797

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[51] Hennig B, Ormsbee L, McClain CJ, et al. Nutrition can modulate the toxicity of environmental pollutants: implications in risk assessment and human health. Environ. Health Perspect. 2012;120(6):771–774. http://www.ncbi.nlm.nih.gov/pubmed/22357258

[52] Ames BN. Optimal micronutrients delay mitochondrial decay and age-associated diseases. Mech. Ageing Dev. 2010;131(7-8):473–479. http://www.ncbi.nlm.nih.gov/pubmed?term=20420847

[53] Gerstner 1977, *op. cit.*

[54] *Ibid.*

[55] Trakhtenberg IM. Chronic effects of mercury on organisms. [Bethesda Md.]: U.S. Dept. of Health Education and Welfare Public Health Service National Institutes of Health; 1974, p 113.

[56] Risher 2003, *op. cit.,* p 4.

[57] Trakhtenberg 1974, *op. cit.*

[58] Gerstner 1977, *op. cit.*

[59] Weiner 1996, *op. cit.*

stimulation; memory loss, particularly short-term memory; neuromuscular changes; headaches; vertigo; visual disturbances; polyneuropathy; deficits in cognitive and motor function; decline in intellectual capacity.

- Psychiatric: emotional lability; nervous excitability; irritability; insomnia; feelings of fear, loss of self-confidence; depression; apathy; social withdrawal.
- Cardiotoxic: coronary insufficiency; palpitations; vascular dystonia; hypertension.
- Immunotoxic: reduced immunity; autoimmunity, allergies.
- Gastroenterological: diarrhea; intestinal disturbances.
- Endocrine: adrenal and thyroid dysfunction.
- Oral: gingivitis; swelling of membranes; metallic taste.
- Skin: red dermographism; increased sweating.
- General: increased fatigue; decreased work capacity; a feeling of impairment.

Uninvestigated anecdotes

The FDA's MedWatch system for reporting adverse effects may be inoperable. Many or perhaps all reports, including those of injured consumers who testified at the 2006 and 2010 FDA hearings, have never been investigated.[60]

The literature contains anecdotal reports of chronic mercury toxicity allegedly from amalgam, including recovery, partial recovery, or cessation of symptoms following removal.[61,62,63,64] According to Chang's *Toxicology of Metals* (1996), "There are a considerable number of individuals who claim they have become ill from their amalgam fillings. It is problematic that so little effort has been made to evaluate such cases thoroughly."[65]

Unknown scope

Many developmental and neurodegenerative diseases appear to be multifactorial, involving a combination of genetic susceptibilities and environmental exposures. Evidence suggests that mercury may play a significant role in such conditions. The diseases for which the evidence is strongest are Alzheimer's,[66] autism,[67,68,69] and Multiple Sclerosis.[70,71,72]

Underreporting

Chronic mercury poisoning is well described in the metals toxicology literature,[73,74] but is not yet recognized by most dentists, physicians or institutions. Thus, patients receive inadequate information from these professionals.[75] Medical textbooks give only superficial coverage to

[60] Personal experience of the author and other injured consumers testifying at the 2010 and 2006 FDA hearings.

[61] Wojcik DP, Godfrey ME, Christie D, Haley BE. Mercury toxicity presenting as chronic fatigue, memory impairment and depression: diagnosis, treatment, susceptibility, and outcomes in a New Zealand general practice setting (1994-2006). Neuro Endocrinol Lett. 27(4):415-23, Aug 2006.

[62] Lygre GB, Gjerdet NR, Björkman L. A follow-up study of patients with subjective symptoms related to dental materials. Community Dent Oral Epidemiol. 33(3):227-34, Jun 2005.

[63] Prochazkova J, Sterzl I, Kucerova H, Bartova J, Stejskal VD. The beneficial effect of amalgam replacement on health in patients with autoimmunity. Neuro Endocrinol Lett. 25(3):211-8, Jun 2004.

[64] Lindh U, Hudecek R, Danersund A, Eriksson S, Lindvall A. Removal of dental amalgam and other metal alloys supported by antioxidant therapy alleviates symptoms and improves quality of life in patients with amalgam-associated ill health. Neuro Endocrinol. Lett. 2002 Dec;23(5-6):459–82. http://www.ncbi.nlm.nih.gov/pubmed?term=12500173

[65] Weiner 1996, *op. cit.*

[66] Mutter 2010, *op. cit.*

[67] Bernard S, Enayati A, Redwood L, Roger H, Binstock T. Autism: a novel form of mercury poisoning. Med. Hypotheses. 2001;56(4):462–471.

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[69] Desoto MC, Hitlan RT. Sorting out the spinning of autism: heavy metals and the question of incidence. Acta Neurobiol Exp (Wars). 2010;70(2):165–176. http://www.ncbi.nlm.nih.gov/pubmed?term=20628440

[70] Aminzadeh KK, Etminan M., Dental amalgam and multiple sclerosis: a systematic review and meta-analysis. J Public Health Dent. Winter;67(1):64-6. Review, 2007.

[71] Bangasi D, Ghadirian P, Ducic S, Morisset R, Ciccocioppo S, McMullen E, Krewski D. Dental amalgam and multiple sclerosis: A case-control study in Montreal, Canada Int J Epidemiol. 27:667–71, 1998.

[72] Bates MN, Fawcett J, Garrett N, Cutress T, Kjellstrom T. Health effects of dental amalgam exposure: a retrospective cohort study. Int J Epidemiol. 33(4):894-902, Aug 2004. Epub May 20, 2004.

[73] Berlin 2007, *op cit.*

[74] Gerstner 1977, *op cit.*

[75] Collective experiences of the Bay Area Chromic Mercury Poisoning Support Group, facilitated by the author.

mercury poisoning, implying that it is found only in occupational or accidental exposures.[76] Standard diagnostic criteria for mercury poisoning usually require a finding of elevated blood or urine mercury.[77] Yet mercury resides only briefly in the blood before migrating to fatty tissues like the brain, where it cannot be measured directly except on autopsy, and where its half-life is estimated in years or decades.[78]

Counterintuitive diagnostic tests

Elevated blood mercury levels reveal only recent, not chronic, exposures.[79] Elevated urine mercury levels reveal kidney burden but not brain retention or toxicity.[80] A susceptible subpopulation with impaired excretion may actually show low mercury levels in blood, urine, hair, and nails, despite a high body burden.[81] In summary, no reliable diagnostic tests have been established for chronic mercury poisoning.[82]

Within the research community, the porphyrins panel is used to reveal with high specificity the unique footprints of certain toxic metals.[83] But since porphyrins are easily destroyed by heat, light, or motion,[84] and since they can also be normalized by antioxidants, the risk of false negatives is high.[85]

[76] Longo DL, Fauci A, Kasper D, et al. eds. Harrison's principles of internal medicine. 18th ed. New York: McGraw-Hill Medical; 2012.

[77] Cecil R. Cecil medicine. 23rd ed. Philadelphia: Saunders Elsevier; 2008.

[78] Mutter J, Naumann J, Sadaghiani C, Walach H, Drasch G. Amalgam studies: disregarding basic principles of mercury toxicity. Int J Hyg Environ Health. 2004;207(4):391–397. http://www.ncbi.nlm.nih.gov/pubmed?term=15471104

[79] Berlin 2007, *op. cit.*

[80] Mutter2004, *op cit.*

[81] Mutter 2006, *op cit.*

[82] Berlin 2007, *op. cit.*

[83] Woods JS. Altered porphyrin metabolism as a biomarker of mercury exposure and toxicity. Can. J. Physiol. Pharmacol. 1996;74(2):210–215. http://www.ncbi.nlm.nih.gov/pubmed?term=8723034

[84] Lord R, Bralley JA. Laboratory evaluations for interpretive and functional medicine. 2nd ed. Duluth, GA: Metametrix Institute; 2008.

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The analogy of lead poisoning

Lead researcher Herbert Needleman warns that the trajectory of mercury science and regulation will likely evolve to resemble that of lead.[86] Lead poisoning was once believed to have only two possible outcomes: death or complete recovery. Later, long-term effects were recognized but thought to occur only in children who had experienced severe encephalopathy. Still later, in the 1970s, children who had displayed no overt symptoms were found to have deficits in cognitive skills, attention, and behavioral control. Modern investigative techniques are still uncovering subtle effects at levels long thought safe.

In the 1960s, the toxic threshold for blood lead was defined as 60 micrograms per deciliter. This standard has dropped repeatedly, falling in 2012 from 10 to 5 micrograms per deciliter. New research involving larger sample sizes, more sensitive outcome measures, and better statistical techniques allow detection of subtle effects at low levels. Such improved research techniques are still in their infancy within mercury research.

In conclusion, mercury's insidious toxic mechanism, in which effects are non-specific, diagnosis is difficult, and damage may be permanent, is enough to justify a ban.

[86] Needleman HL. Mercury in dental amalgam--a neurotoxic risk? JAMA. 2006;295(15):1835–1836. http://www.ncbi.nlm.nih.gov/pubmed?term=PMID%3A%20%20%20%20%2016622146

Exposures

Dental amalgam releases mercury vapor continuously. The amount varies widely, depending on the exact chemical properties and physical partial sizes within the amalgam, and on the oral environment -- chewing, brushing, bruxism, oral temperature and pH, oral vacuum, and proximity to other metals.[87] The exposure to mercury may be highly variable even for individuals with comparable amounts of amalgam fillings.[88]

An estimated 80% is absorbed into the bloodstream,[89] with reported values ranging from 61 to 86%.[90]

According to the World Health Organization, amalgam-bearers absorb on average 3 to 17 micrograms of mercury per day,[91] with wide individual variably, documented at up to 100 micrograms per day.[92] Chewing and tooth-brushing may cause a transient five-fold increase in mercury exposure.[93] According to a 1993 Public Health Service report, the majority of amalgam-bearers incur exposures of 5 micrograms or less per day.[94] This is the value underlying the FDA's risk assessment.[95] The FDA's 2010 science advisory panel urged the FDA to use a distribution covering a range of exposures, rather than an average.[96]

Estimates of average mercury exposure from amalgam generally fall below levels known to cause clinical effects in healthy, occupationally exposed adults. However, these study subjects are healthier than the population at large. In addition, many amalgam-bearers appear to incur exposures in excess of the averages assumed by the FDA and others.

Fish mercury

Fish contains methylmercury, a type of organic (carbon-containing) mercury. The toxicity of

[87] Cartland RJ. The US dental amalgam debate: 2010 meeting of the FDA dental products panel. 2012, p 8. http://iaomt.org/wp-content/uploads/Cartland-US-Dental-Amalgam-Debate-2010-FDA-Meeting-2012-11-18.pdf

[88] Weiner 1996, *op. cit*.

[89] Agency for Toxic Substances and Disease Registry (ATSDR) and Research Triangle Institute, Toxicological profile for mercury, U.S. Dept. of Health and Human Services, Public Health Service, Atlanta, Georgia, 1999. http://www.atsdr.cdc.gov/toxprofiles/tp46.pdf

[90] Richardson GM, Allard D, Douma S, Graviere J, Purtill C and Wilson R. Amalgam Risk Assessment, Final Report to the International Academy of Oral Medicine and Toxicology. Mercury Exposure and Risks From Dental Amalgam, Part 1: Updating Exposure Re-examining Reference Exposure Levels, and Critically Evaluating Recent Studies. November 8, 2010. 2010 Meeting Materials of the Dental Products Panel, Non-FDA Generated, Gaithersburg, MD, December 14-15, 2010. http://iaomt.org/wp-content/uploads/Cartland-US-Dental-Amalgam-Debate-2010-FDA-Meeting-2012-11-18.pdf

[91] Two WHO criteria documents present identical information:

> International Programme on Chemical Safety. Methylmercury (Environmental health criteria document 101). Geneva: World Health Organization; 1990, Table 4 in section 5.2.1. http://www.inchem.org/documents/ehc/ehc/ehc101.htm
>
> International Programme on Chemical Safety. Inorganic Mercury (Environmental health criteria document 118). Geneva: World Health Organization; 1991, Table 2 in section 5.1.1.1. http://www.inchem.org/documents/ehc/ehc/ehc118.htm

[92] Barregård L, Sällsten G, Järvholm B. People with high mercury uptake from their own dental amalgam fillings. Occup Environ Med. 1995;52(2):124–128. http://www.ncbi.nlm.nih.gov/pubmed?term=PMID%3A%20%20%20%20%207757165

[93] *Ibid*. citing Richardson GM (1995) Assessment of mercury exposure and risksfrom dental amalgam. Ottawa, Ontario, Health Canada, Environmental Health Directorate, Medical Devices Bureau; and Sallsten G, Thoren J, Barregard L, Schutz A, Skarping G (1996) Long-term use of nicotine chewing gum and mercury exposure from dental amalgam fillings. Journal of Dental Research, 75(1):594–598.

[94] Risher 2003, op. cit., p 11, provides discussion of the range of estimates in the literature.

[95] Dental Amalgam: A Scientific Review and Recommended Public Health Service Strategy for Research, Education and Regulation; Public Health Service, U.S. Department of Health and Human Services, Appendix III, page 22 of 28, January 1993. http://www.health.gov/environment/amalgam1/ct.htm.

[96] US Food and Drug Administration, December 15, 2010: Meeting Transcript, 2010 Meeting Materials of the Dental Products Panel, FDA Generated, Gaithersburg, MD, December 14-15, 2010. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/DentalProductsPanel/UCM242363.pdf

methylmercury is similar to that for elemental mercury vapor -- both are lipophilic, thus travel easily throughout the body, and readily cross cell membranes including the blood-brain barrier. Both oxidize into inorganic mercury (Hg^{2+}), which is lipophobic and thus becomes trapped inside the cells.[97]

Fish mercury is found primarily in the muscle or protein.[98] Due to bioaccumulation up the food chain, the concentration of mercury in fish is one million to ten million times greater than that in surrounding waters.[99] Fish has one thousand to ten thousand times the mercury concentration found in other food sources.[100]

The EPA sets a regulatory standard for chronic merhylmercury ingestion, called the reference dose, of 1 x 10^{-4} milligrams per kilogram-body-weight per day[101] (or 0.1 micrograms per kilogram-body-weight per day); thus a 65 kg (143 pound) adult could tolerate up to 6.5 micrograms per day of fish mercury. A 48 kg (106 pound) adult could tolerate up to 4.8 micrograms per day of fish mercury -- which is the same level that the EPA calculates for chronic exposure to mercury vapor. (0.3 micrograms per m3 * 20 m3 per day * 80% absorption = 4.8 micrograms per day.)

Note that these regulatory safety standards presume a single source of exposure, not multiple routes -- i.e., not *both* 4.8 mcgd/d from fish *and* 4.8 mcg/d from amalgams.

The FDA sets a regulatory standard, called the Action Level, for methylmercury in commercial fish, of 1 part per million (ppm).[102] Typical concentrations or mercury in fish range from less than 0.1 ppm for low-mercury fish to more than 1.0 ppm for high-mercury fish.[103] Consumption of low-mercury fish, at 0.1 ppm, would allow an intake of 65 grams per day or 16 ounces per week, equivalent to two large servings per week. But consumption of high-mercury fish, at 1.0 ppm methylmercury, would allow an intake of only 6.5 grams per day or 1.6 ounces per week, equivalent to only about one meal per month.

Both the FDA and the EPA advise women who may become pregnant, pregnant women, nursing mothers, and young children to avoid or restrict some types of fish.[104]

Exposure to mercury vapor from amalgam varies widely, from 1 to 100 mcg/d, with regulators in the past having assumed an average of 5 mcg/d, which may be optimistic. Thus, fish advisories that recommend an allowable number of fish meals per time-period are numerically equivalent to having a low to average amount of amalgam exposure.

[97] Berlin 2007, *op cit.*

[98] EPA Fact Sheet: Mercury Update: Impact on Fish Advisories. June 2001. http://water.epa.gov/scitech/swguidance/fishshellfish/outreach/upload/2001_05_31_fish_advice_mercupd.pdf

[99] *Ibid.*

[100] *Ibid.*

[101] US Environmental Protection Agency Integrated Risk Information System. Methylmercury. http://www.epa.gov/iris/subst/0073.htm

[102] FDA webpage: Action Levels for Poisonous or Deleterious Substances in Human Food and Animal Feed. http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/ChemicalContaminantsandPesticides/ucm077969.htm#merc

[103] US Food and Drug Adminsitration webpage: Mercury Levels in Commercial Fish and Shellfish http://www.epa.gov/iris/subst/0073.htm

[104] US Food and Drug Administration and US Environmental Protection Agenay. News release. Mardch 19, 2004. FDA and EPA announce the revised consumer advisory on methylmercury in fish. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2004/ucm108267.htm

Violations of existing laws and standards

Environmental health standards

Regulatory standards are typically developed using published studies of occupationally exposed, healthy, working adults. A "Lowest Observable Adverse Effects Level" (LOAEL) is identified, and Uncertainty Factors are applied to cover dataset uncertainties, vulnerable subpopulations, and individual variability. Much scientific debate surrounds the choice of the LOAEL and the quantification of the uncertainty factors.[105]

The above exposure estimates can be compared to the regulatory standards (which use units of mass per cubic meter of air), using standard assumptions of 20 cubic meters of air inhaled per day, and 80% absorption, as summarized in Table 1.

EPA RfC

The US EPA Inhalation Reference Concentration (RfC) for chronic inhalation of mercury vapor, published in 1995, is 0.3 micrograms per cubic meter of air.[106] (In light of more recent data, the adequacy of this standard was questioned by the 2010 FDA science advisory panel.[107])

ATSDR MRL

The US Agency for Toxic Substances and Disease Registry (ATSDR) Minimal Risk Level (MRL) for chronic inhalation of mercury vapor, published in 1999, is 0.0002 milligrams per cubic meter of air (i.e., 0.2 micrograms per m^3).[108]

CalEPA REL

The CalEPA chronic Reference Exposure Level (REL) for mercury vapor, published in 2008, is 0.03 micrograms per cubic meter of air.[109] Incidentally, A 2010 risk assessment using a more recent study (with lower LOAEL) and lower Uncertainty Factors than did CalEPA, arrived at a similar value -- 0.07 micrograms per m^3.[110]

Given the wide range of exposures, the standards appear to provide little or no margin of safety for much of the population. This concern is echoed in Chang's *Toxicology of Metals* (1996)

> *Comparison of data on the release and uptake of mercury from amalgam fillings with available human and animal data on the toxicity of inorganic mercury indicates that the level of exposure to mercury from amalgam fillings*

[105] For example, since chlorine oxidizes mercury into a less absorbable form, the appropriateness of using studies of chlor-alkali workers, which may understate risk, is debated. EPA and ATSDR use an Uncertainty Factor of 30; while CalEPA uses 300. Yet Lettmerir (2010) uses an occupational gold-mining study, finds a lower LOAEL, applies an Uncertainty Factor of 50, and recommends a standard of 0.07 micrograms/m3, which is similar to the CalEPA standard, which used a higher LOAEL and a higher Uncertainty Factor. Cartland RJ. The US dental amalgam debate: 2010 meeting of the FDA dental products panel. 2012, p 12. http://iaomt.org/wp-content/uploads/Cartland-US-Dental-Amalgam-Debate-2010-FDA-Meeting-2012-11-18.pdf citing Lettmeier B, Boese-O'Reilly S, Drasch G. 2010. Proposal for a revised reference concentration (RfC) for mercury vapour in adults. Sci Total Environ, 408: 3530-3535, 2010. http://www.ncbi.nlm.nih.gov/pubmed/20576543

[106] US EPA: http://www.epa.gov/iris/subst/0370.htm

[107] FDA meeting transcript. Dec. 15, 2010. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/DentalProductsPanel/UCM242363.pdf

[108] Agency for Toxic Substances and Disease Registry (ATSDR) and Research Triangle Institute, Toxicological profile for mercury, U.S. Dept. of Health and Human Services, Public Health Service, Atlanta, Georgia, 1999, p 509. http://www.atsdr.cdc.gov/toxprofiles/tp46.pdf

[109] CalEPA OEHHA: http://oehha.ca.gov/air/toxic_contaminants/pdf_zip/Mercury_postSRP3.pdf

[110] Lettmeier B, Boese-O'Reilly S, Drasch G. Proposal for a revised reference concentration (RfC) for mercury vapour in adults. Sci. Total Environ. 2010;408(17):3530–3535. http://www.ncbi.nlm.nih.gov/pubmed?term=20576543

should be of serious concern.[111]
(Emphasis added.)

A 2011 study confirms that tens of millions of Americans are likely to incur exposures from their amalgams in excess of the EPA standard; and twice as many incur exposures in excess of the CalEPA standard.[112]

Occupational health

Many studies of dental workers have found sub-clinical or pre-clinical health effects as compared to controls despite exposures that appear to be below current occupational health standards. This suggests that these standards are not adequately health protective. Alternatively, the exposure metrics are not reliable indicators of exposure or body burden. Indeed, in many cases the authors have used metrics that are now known to be unreliable, but this does not negate the conclusion that dentists may incur subtle health effects at exposures once presumed safe.

- A 2011 study by Neghab *et al.* of 106 dentists and 94 controls in Iran found that neuropsychological, muscular, respiratory, cardiovascular and dermal symptoms were more prevalent in dentists. Office mercury levels for the dentists were not high; the mean was about 3 micrograms per cubic meter of air. The dentists' urinary mercury levels were not elevated; the mean was about 3 micrograms per gram creatinine.[113]
- A 2002 study by Ritchie *et al.* of 180 dentists and 180 controls in Scotland found that dentists were more likely than controls to have kidney disorders, memory disturbances, and psychomotor deficits. These effects were not associated with mercury levels measured in urine, hair, or nails. (The authors seem unaware that these are not reliable metrics for mercury body burden.) All but one of the dentists had urinary mercury levels below the regulatory guidance value.[114,]
- A 1998 study by Echeverria, Woods, Bitner, *et al.* of 34 male dentists and 15 female dental assistants found subtle preclinical effects on health symptoms, mood, motor function, and cognition, associated with Hg body burden. The metric for body burden was the urine mercury level after a DMPS chelation challenge. The authors believe the subjects incurred low exposure based on their pre-challenge urine mercury levels, which were less than 4 micrograms per liter. (Incidentally, the authors seem unaware that both pre- and post-challenge urine mercury levels are not reliable metrics for body burden.)[115]
- A 1998 pooled study by Bittner, Echeverria, Woods, *et al.* of 230 subjects based on six previous studies... .[116]

[111] Weiner 1996, *op. cit.*

[112] Richardson GM, Wilson R, Allard D, et al. Mercury exposure and risks from dental amalgam in the US population, post-2000. Sci. Total Environ. 2011;409(20):4257–4268. http://www.ncbi.nlm.nih.gov/pubmed/21782213x

[113] Neghab M, Choobineh A, Hassan Zadeh J, Ghaderi E. Symptoms of intoxication in dentists associated with exposure to low levels of mercury. Ind Health. 2011;49(2):249–254. http://www.ncbi.nlm.nih.gov/pubmed?term=PMID%3A%20%20%20%20%2021173523

[114] Ritchie KA, Gilmour WH, Macdonald EB, Burke FJT, McGowan DA, Dale IM, et al. Health and neuropsychological functioning of dentists exposed to mercury. Occup Environ Med. 2002 May;59(5):287–93. http://www.ncbi.nlm.nih.gov/pubmed?term=11983843

[115] Echeverria D, Aposhian HV, Woods JS, Heyer NJ, Aposhian MM, Bittner AC Jr, et al. Neurobehavioral effects from exposure to dental amalgam Hg(o): new distinctions between recent exposure and Hg body burden. FASEB J. 1998 Aug;12(11):971–80. http://www.ncbi.nlm.nih.gov/pubmed?term=9707169

[116] Bittner AC Jr, Echeverria D, Woods JS, Aposhian HV, Naleway C, Martin MD, et al. Behavioral effects of low-level exposure to Hg0 among dental professionals: a cross-study evaluation of psychomotor effects. Neurotoxicol Teratol. 1998 Aug;20(4):429–39. http://www.ncbi.nlm.nih.gov/pubmed/9697969

- A 1997 study by Langworth *et al.* of 22 dentists and 22 dental assistants....[117]
- A 1995 study by Ritchie *et al.* of .[118]
- A 1995 study by Echeverria, Bittner, Woods, *et al.* of.[119]
- A 1993 study by Foo, Ngim, *et al.* of .[120,]
- A 1992 study by Ngim, Foo, *et al.* of .[121]
- A 1986 study by Uzzell and Oler of 13 female dental workers found that chronic, subtoxic levels of mercury appear to produce mild changes in short-term nonverbal recall and heightened distress generally, and particularly in categories of obsessive compulsion, anxiety and psychoticism, without alterations in general intellectual functioning, attention, verbal recall, and motor skills. .[122]
- A 1982 study by Shapiro, Uzzell, *et al.* of .[123]

[117] Langworth S, Sällsten G, Barregård L, Cynkier I, Lind ML, Söderman E. Exposure to mercury vapor and impact on health in the dental profession in Sweden. J. Dent. Res. 1997 Jul;76(7):1397–404. http://www.ncbi.nlm.nih.gov/pubmed?term=9207773

[118] Ritchie KA, Macdonald EB, Hammersley R, O'Neil JM, McGowan DA, Dale IM, et al. A pilot study of the effect of low level exposure to mercury on the health of dental surgeons. Occup Environ Med. 1995 Dec;52(12):813–7. http://www.ncbi.nlm.nih.gov/pubmed?term=8563844

[119] Echeverria D, Heyer NJ, Martin MD, Naleway CA, Woods JS, Bittner AC Jr. Behavioral effects of low-level exposure to elemental Hg among dentists. Neurotoxicol Teratol. 1995 Apr;17(2):161–8. http://www.ncbi.nlm.nih.gov/pubmed?term=7760775

[120] Foo SC, Ngim CH, Salleh I, Jeyaratnam J, Boey KW. Neurobehavioral effects in occupational chemical exposure. Environ. Res. 1993 Feb;60(2):267–73. http://www.ncbi.nlm.nih.gov/pubmed/8472657

[121] Ngim CH, Foo SC, Boey KW, Jeyaratnam J. Chronic neurobehavioural effects of elemental mercury in dentists. Br J Ind Med. 1992 Nov;49(11):782–90. http://www.ncbi.nlm.nih.gov/pubmed/1463679

[122] Uzzell BP, Oler J. Chronic low-level mercury exposure and neuropsychological functioning. J Clin Exp Neuropsychol. 1986 Oct;8(5):581–93. http://www.ncbi.nlm.nih.gov/pubmed?term=3805254

[123] Shapiro IM, Cornblath DR, Sumner AJ, Uzzell B, Spitz LK, Ship II, et al. Neurophysiological and neuropsychological function in mercury-exposed dentists. Lancet. 1982 May 22;1(8282):1147–50. http://www.ncbi.nlm.nih.gov/pubmed?term=6122938

Occupational exposures

A 2003 review found that respirable mercury particulate matter released into air during amalgam removal is the predominant source of daily mercury exposure for practicing dentists.[124] At least 65% of the amalgam particulate matter is less than one micron in diameter, thus readily passes through most dental masks.[125] Short-term air concentrations routinely reach 100 micrograms per cubic meter, and can reach 2500 micrograms per cubic meter.[126] Using standard assumptions, the author estimates that a dentist doing four amalgam removals in a typical day would receive a dose of 38,000 micrograms of mercury via inhaled particulate, and about 67 micrograms of mercury via inhaled vapor.[127]

A 1973 study found that mist during drilling resulted in high concentrations of mercury in the heart, liver, brain, and kidney that failed to normalize after 72 hours.[128]

The extremely high exposures incurred during amalgam placement and removal have not been considered by the FDA in its regulation of amalgam.[129] Further, recent attempts by IAOMT dentists to remove amalgam with minimal exposure indicate that it may be impossible to

[124] Richardson GM. Inhalation of Mercury-Contaminated Participate Matter by Dentists: An Overlooked Occupational Risk. Human and Ecological Risk Assessment: An International Journal. 2003; 9(6):1519–31. Available from: http://www.tandfonline.com/doi/abs/10.1080/10807030390251010 Richardson cites Richards JM, Warren PJ. Mercury vapour released during the removal of old amalgam restorations. Br Dent J. 1985 Oct 5;159(7):231–2; and Buchwald H. Exposure of dental workers to mercury. Am Ind Hyg Assoc J. 1972 Jul;33(7):492–502.

[125] *Ibid.*

[126] *Ibid.*

[127] *Ibid.*

[128] Cutright DE, Miller RA, Battistone GC, Milikan LJ. Systemic mercury levels caused by inhaling mist during high-speed amalgam grinding. J Oral Med. 1973;28(4):100–104. http://www.ncbi.nlm.nih.gov/pubmed?term=PMID%3A%20%20%20%20%204586988

[129] IAOMT news, February 13, 2012, http://iaomt.org/holdup-fda-fda-webview-know/, citing FDA Webview, http://www.fdaweb.com/default.php?ea=v&aid=D5120790&cate=PS.

Table 1: The mid to upper range of exposures from amalgams exceeds many safety standards and all exposures from amalgams appear to exceed the CalEPA standard.

	micrograms of mercury per day	micrograms of mercury per cubic meter of air
Exposures		
average chronic exposure from amalgam	3 to 17	
FDA's typical chronic exposure from amalgam	5	
high-end chronic exposure from amalgam	100	
short-term exposure to mercury vapor to dental staff during amalgam removal	67	~ 100
short-term exposure to mercury from particulate matter to dental staff during amalgam removal	38,000	~ 100 to 2500
Regulatory standards:		
Chronic		
US EPA RfC for chronic mercury inhalation (1995)	4.8 (equivalent)	0.3
US ATSDR MRL for chronic mercury inhalation (1999)	3.2 (equivalent)	0.2
Cal EPA chronic REL (2008)	0.48 (equivalent)	0.03
NIOSH REL	190 (equivalent)	50 (for up to 40 h/week)
ACGIH TLV	95 (equivalent)	25 (for up to 40 h/week)
Acute		
OSHA PEL	--	100 (instantaneous)
EPA/ASTDR Action Level prompting evacuation after a spill		10
Cal EPA acute REL (2008)	--	0.6 (one hour)

emove amalgam without violating the OSHA PEL.[130]

The website MercuryExposure.Info has information that can help dental employees understand their rights to a safe workplace under OSHA.

Occupational health standards

Occupational health standards appear to be unenforced within dentistry. The following standards are described on the Occupational Safety and Health Administration (OSHA) website:[131]

OSHA PEL

The current OSHA permissible exposure limit (PEL) for mercury vapor is 0.1 milligram per cubic meter of air (*i.e.,* 100 micrograms per m^3), as a ceiling limit. "A worker's exposure to mercury vapor shall at no time exceed this ceiling level."[132]

NIOSH REL

The National Institute for Occupational Safety and Health (NIOSH) has established a recommended exposure limit (REL) for mercury vapor of 0.05 mg/m^3 (*i.e.* 50 mcg/m^3), as a time-weighted average (TWA) for up to a 10-hour workday and a 40-hour workweek.

ACGIH TLV

The American Conference of Governmental Industrial Hygienists (ACGIH) has assigned mercury vapor a threshold limit value (TLV) of 0.025 mg/m^3 (*i.e.* 25 mcg/m^3), as a time-weighted average (TWA) for a normal 8-hour workday and a 40-hour workweek.

These workplace inhalation exposure standards can be converted to the continuous (environmental) exposure standards shown in the table by assuming an inhalation rate of 20 m^3 per day, with exposure of 40 hours/168 hours and an 80% absorption rate, to yield the values shown.

Legal inconsistencies

Dentists may place amalgam in only three places: a patient's teeth; a hazardous waste facility; or a sealed amalgam recycling container. Yet informed consent is not required for placement in teeth.

Proposition 65

Although mercury is listed as a reproductive toxin under California's Proposition 65, the law does not apply to businesses with less than ten employees.

[130] (cite current IAOMT experiment when published)

[131] OSHA website. http://www.osha.gov/SLTC/healthguidelines/mercuryvapor/recognition.html

[132] *Ibid.*

The mix of evidence

The body of animal evidence has long suggested that mercury toxicity is linear and cumulative, with no apparent safe threshold. But policymakers prefer to look to human evidence. Human epidemiological studies usually find no significant association between amalgams and clinical health effects. However, chronic low-dose toxins with long latencies are difficult to study. Yet as investigative methods improve, evidence of human harm is emerging.

Animal evidence (incomplete)

In the 1990s, sheep and monkey studies using radiolabeled mercury dental amalgam showed mercury accumulating in the digestive tract, kidneys, liver, fetus, breast milk, and other tissues.[133,134,135,136]

Mercury from dental amalgam can increase the prevalence of antibiotic resistant bacteria in the intestines of primates.[137]

[133] Hahn LJ, Kloiber R, Vimy MJ, Takahashi Y, Lorscheider FL. Dental "silver" tooth fillings: a source of mercury exposure revealed by whole-body image scan and tissue analysis. FASEB J. 1989;3(14):2641–2646. http://www.ncbi.nlm.nih.gov/pubmed?term=2636872

[134] Hahn LJ, Kloiber R, Leininger RW, Vimy MJ, Lorscheider FL. Whole-body imaging of the distribution of mercury released from dental fillings into monkey tissues. FASEB J. 1990;4(14):3256–3260. http://www.ncbi.nlm.nih.gov/pubmed/2227216

[135] Vimy MJ, Takahashi Y, Lorscheider FL. Maternal-fetal distribution of mercury (203Hg) released from dental amalgam fillings. Am. J. Physiol. 1990;258(4 Pt 2):R939–945. http://www.ncbi.nlm.nih.gov/pubmed/2331037

[136] Vimy MJ, Hooper DE, King WW, Lorscheider FL. Mercury from maternal "silver" tooth fillings in sheep and human breast milk. A source of neonatal exposure. Biol Trace Elem Res. 1997;56(2):143–152. http://www.ncbi.nlm.nih.gov/pubmed/2331037

[137] Summers A, Wireman J, Vimy, MJ, Lorscheider, FL, Marshall B, Levy SB, Bennett S, Billard L. Mercury Released from Dental "Silver" Fillings Provokes an Increase in Mercury- and Antibiotic-Resistant Bacteria in Oral and Intestinal Floras of Primates, Antimicrob Agents Chemother, 37(4):825-834, 1993. http://www.ncbi.nlm.nih.gov/pubmed?term=8280208

The body of animal evidence suggests that mercury toxicity is linear and cumulative, with no apparent safe threshold.

Human autopsy and biopsy evidence (incomplete)

A 1999 biopsy study of 13 patients with idiopathic dilated cardiomyopathy found 10,000 times the mercury concentration in heart tissue, compared to controls.[138]

A 1989 autopsy study of 8 dental staff and 27 controls found that dental staff had high levels of mercury in certain tissues, particularly the pituitary.[139]

A 1987 autopsy study of 34 adult subjects found that mercury levels in brain tissue were correlated with the number of amalgam fillings.[140,141]

Epidemiological studies

Many epidemiological studies of amalgam have failed to find a statistically significant association with clinical effects. Indeed, studies often show poor correlations between amalgam and body

[138] Frustaci A, Magnavita N, Chimenti C, et al. Marked elevation of myocardial trace elements in idiopathic dilated cardiomyopathy compared with secondary cardiac dysfunction. J. Am. Coll. Cardiol. 1999;33(6):1578–1583. http://www.ncbi.nlm.nih.gov/pubmed/10334427

[139] Nylander M, Friberg L, Eggleston D, Björkman L. Mercury accumulation in tissues from dental staff and controls in relation to exposure. Swed Dent J. 1989;13(6):235–243. http://www.ncbi.nlm.nih.gov/pubmed/2603127

[140] Nylander M, Friberg L, Lind B. Mercury concentrations in the human brain and kidneys in relation to exposure from dental amalgam fillings. Swed Dent J. 1987;11(5):179–187. http://www.ncbi.nlm.nih.gov/pubmed/3481133

[141] D. W. Eggleston, M. Nylander, Correlation of dental amalgam with mercury in brain tissue, J Prosthet Dent 58, 704–707 (1987). http://www.ncbi.nlm.nih.gov/pubmed?term=3480359

burden, and also between body burden and health symptoms. This situation has led some to view the controversy as a hoax or a psychiatric issue, while others view genetic susceptibilities as a likely explanation for these counterintuitive results.

Inherent imprecision of mercury exposure assessment

The key problem with human studies of dental amalgams, or mercury in general, is the impossibility of assessing mercury exposure or body burden. For most people, the predominant sources are dental amalgam and dietary fish intake, both of which are often difficult to quantify over past years or a lifetime. Toxicological theory indicates that prenatal exposures form maternal amalgams and diet may be a significant source, yet is usually unquantifiable. Many studies simply measure the numbe of amalgams or amalgam surfaces at a point in time, ignoring other exposures. Yet without adequate exposure assessment, the results of an epidemiological investigation will be biased toward the null.[142]

Other biases in epidemiology

Epidemiology is best suited to investigate associations between hazards that can be adequately quantified, and health outcomes that are clear or specific. It is less well-suited to investigate associations between chronic, low-dose toxicants, and health effects that are myriad and nonspecific, especially when unidentified genetic susceptibilities are involved. Attaining adequate statistical power in these circumstances would require unrealistically large numbers of subjects.

In addition to in adequate exposure assessments, common short-cuts in epidemiology which are usually found in amalgam studies include:[143]

- selection bias (in occupational studies, the healthy-worker effect), which overlooks vulnerable or unhealthy subpopulations;
- limited durations, which overlook effects that may take decades to develop; and
- low statistical power, which overlooks uncommon effects.

These biases may be unavoidable, but they nonetheless bias the results toward the null, masking any real associations.

Misleading information in the amalgam literature

Many amalgam studies simply investigate associations between blood or urine mercury levels and health effects, often finding none. The fact that such studies are published may imply that blood or urine mercury levels are meaningful, yet current science suggests they are not. Such studies ignore basic principles of mercury toxicity:[144,145,146]

- Blood and urine mercury levels show poor correlations with body burden;
- Body burden, though difficult to assess, appears poorly correlated with symptoms;
- Studies in which a “half-life” in the body is reported imply that mercury is excreted at a knowable, exponentially decreasing rate. Yet excretion is both tissue-specific and time/age dependent, reflecting cumulative impairments to detoxification and varying nutritional status.
- Most epidemiological studies of mercury are unable to adequately assess total exposures or body burden as described above, since exposures may

[142] Grandjean P, Budtz-Jørgensen E. Total imprecision of exposure biomarkers: implications for calculating exposure limits. Am. J. Ind. Med. 2007;50(10):712–719. http://www.ncbi.nlm.nih.gov/pubmed?term=17492658

[143] Weiner 1996, *op. cit*.

[144] Mutter 2006, *op. cit.*

[145] Mutter 2007, *op. cit.*

[146] Berlin 2007, *op. cit.*

accumulate over a lifetime including prenatally.[147]

Key studies finding an association

A 2012 study of 600 dentists and 600 matched controls, based on pharmacy records, found that the dentists demonstrated significantly more prescription utilization of medications, including the following illness categories: neuropsychological, neurological, respiratory, and cardiovascular.[148]

A 2009 study of 100 autistic children found that severe autism was associated with 6 or more maternal dental amalgams during pregnancy.[149]

A 2008 study of 39 non-smoking women aged 40-45 found that amalgam is associated with hearing loss.[150] The authors note, "This provides further argument for the use of amalgams to be phased out where suitable alternatives exist."

A 2004 study of 194 male dentists and 233 female dental assistants found that urinary mercury levels were associated with nine measures of cognitive and motor effects in the dentists and eight measures in the dental assistants. The BDNF variant was associated with four measures in dentists, and three measures in dental assistants in an additive manner.[151]

A 2004 retrospective cohort study of 20,000 New Zealand military personnel used dental records over twenty years and found a slight association between amalgam-surface-years and Multiple Sclerosis (adjusted hazard ratio of 1.24, p=0.06), but not other diseases studied.[152] Since 85% of subjects were 45 years or under at the end of the study, chronic diseases of aging would not have been adequately captured by this study. Further, since health outcomes were based only on hospitalization records, illnesses not requiring hospitalization would not have been adequately captured. The authors note, "The possibility that multiple sclerosis could be associated with dental amalgams deserves further investigation."

A 1998 study of 49 dentists and dental assistants found subtle pre-clinical effects on mood, motor function, and cognition, associated with mercury body burden as indicated by chelation-challenged urinary mercury levels, but not with unchallenged urinary mercury levels.[153]

A 1997 Swedish study of 22 dentists, 22 dental assistants, and 44 matched controls found an association with some neurobehavioral effects even at occupational exposures that were considered low.[154]

A 1995 study of 19 exposed and 20 unexposed dentists found that low scores on various neurobehavioral tests were correlated with urine mercury levels and urine porphyrins levels.[155]

A 1992 study of 98 dentists and 54 controls found the dentists' neurobehavioral test performance was significantly worse than that of the controls, even though their exposures were within the Threshold Limit Values set by the

[147] Grandjean and Budtz-Jørgensen, 2007, *op cit.*

[148] Duplinsky TG, Cicchetti DV. The Health Status of Dentists Exposed to Mercury from Silver Amalgam Tooth Restorations. International Journal of Statistics in Medical Research. 2012;1(1):1–15. http://iaomt.org/duplinsky-2012-health-status-dentists-exposed-mercury-silver-amalgam-tooth-restorations/

[149] Geier DA, Kern JK, Geier MR. A prospective study of prenatal mercury exposure from maternal dental amalgams and autism severity. Acta Neurobiologiae Experimentalis. 69(2):189-97, 2009. http://www.ncbi.nlm.nih.gov/pubmed?term=19593333

[150] Rothwell JA, Boyd PJ. Amalgam dental fillings and hearing loss. Int J Audiol. 47(12):770-6, Dec 2008. http://www.ncbi.nlm.nih.gov/pubmed?term=19085401

[151] Echeverria2005, *op cit.*

[152] Bates MN, Fawcett J, Garrett N, Cutress T, Kjellstrom T. Health effects of dental amalgam exposure: a retrospective cohort study. Int J Epidemiol. 33(4):894-902, Aug 2004. http://www.ncbi.nlm.nih.gov/pubmed/15155698

[153] Echeverria D, Aposhian HV, Woods JS, et al. Neurobehavioral effects from exposure to dental amalgam Hg(o): new distinctions between recent exposure and Hg body burden. FASEB J. 1998;12(11):971–980. http://www.ncbi.nlm.nih.gov/pubmed?term=9707169

[154] Langworth S, Sällsten G, Barregård L, et al. Exposure to mercury vapor and impact on health in the dental profession in Sweden. J. Dent. Res. 1997;76(7):1397–1404. http://www.ncbi.nlm.nih.gov/pubmed?term=9207773

[155] Echeverria D, Heyer NJ, Martin MD, et al. Behavioral effects of low-level exposure to elemental Hg among dentists. Neurotoxicol Teratol. 1995;17(2):161–168. http://www.ncbi.nlm.nih.gov/pubmed/7760775

Occupational Safety and Health Administration.[156]

Key studies not finding an association

A 2005 study of a 1997-98 database of 1663 Vietnam-era veterans found no association between amalgam and clinical neurological symptoms.[157] However, a significant association was found between amalgam and the "continuous vibrotactile sensation response," which was deemed subclinical. Weaknesses of the study include: The exposure variable -- current number of amalgam surfaces -- fails to capture mercury body burden. And the non-elderly dataset fails to represent the population as a whole. Genetic susceptibilities were also unaddressed. Finally, the database did not include more sensitive measures such as nerve conduction studies.

A 2003 study of 550 working adults, aged 30-49, found no association between exposure and neuropsychological test scores.[158] Exposure was measured as both amalgam-surfaces and as urinary mercury. Weaknesses include: The healthy-worker dataset fails to represent the population as a whole.

Randomized, controlled clinical trials: Children's Amalgam Trials

The only randomized, controlled, clinical trials for amalgam to date are two studies known as the Children's Amalgam Trials. Beginning in 1996, one trial was held in New England, and the other in Portugal, both with funding from the National Institute of Dental and Craniofacial Research within the National Institutes of Health.[159] In New England, 534 children without amalgam were randomly assigned to an amalgam or composite group, and then tested annually for five years.[160] In Portugal, 507 children were also randomly assigned to an amalgam or composite group and then tested annually for seven years.

Initial results from both studies, published in 2006, found no significant difference in various measures of neurobehavioral health between the amalgam group and the composite group, although both studies found higher urinary mercury in the amalgam group.[161,162]

This pair of studies has been cited by the ADA and the FDA as providing evidence that amalgams are safe.[163,164] But recent findings show dose-related harm, especially to a genetically susceptible subset of children, as follows.

In 2011, another team reanalyzed the Portugal dataset, dividing the amalgam group into high, medium, and low levels of amalgam. Statistical analysis of the resulting four groups (instead of

[156] Ngim CH, Foo SC, Boey KW, Jeyaratnam J. Chronic neurobehavioural effects of elemental mercury in dentists. Br J Ind Med. 1992;49(11):782–790. http://www.ncbi.nlm.nih.gov/pubmed?term=1463679

[157] Kingman A, Albers JW, Arezzo JC, Garabrant DH, Michalek JE. Amalgam exposure and neurological function, Neurotoxicology. 26(2):241-55, Mar 2005. http://www.ncbi.nlm.nih.gov/pubmed/15713345

[158] Factor-Litvak P, Hasselgren G, Jacobs D, et al. Mercury derived from dental amalgams and neuropsychologic function. Environ. Health Perspect. 2003;111(5):719–723. http://www.ncbi.nlm.nih.gov/pubmed?term=12727600

[159] NIH News, April 18, 2006. http://www.nih.gov/news/pr/apr2006/nidcr-18.htm

[160] Anon. The Children's Amalgam Trial: design and methods. Control Clin Trials. 2003;24(6):795–814. http://www.ncbi.nlm.nih.gov/pubmed?term=PMID%3A%20%20%20%20%2014662283

[161] Bellinger DC, Trachtenberg F, Barregard L, et al. Neuropsychological and renal effects of dental amalgam in children: a randomized clinical trial. JAMA. 2006;295(15):1775–1783. http://www.ncbi.nlm.nih.gov/pubmed?term=PMID%3A%20%20%20%20%2016622139

[162] DeRouen TA, Martin MD, Leroux BG, et al. Neurobehavioral effects of dental amalgam in children: a randomized clinical trial. JAMA. 2006;295(15):1784–1792. http://www.ncbi.nlm.nih.gov/pubmed?term=derouen%20JAMA%202006

[163] American Dental Association. What Others Say. 2008. http://www.ada.org/sections/publicResources/pdfs/others.pdf

[164] According to the FDA 2009 Summary of Changes to the Classification of Dental Amalgam and Mercury, "two clinical trials in children aged six and older did not find neurological or renal injury associated with amalgam use," (citing the two 2006 JAMA articles on the Children's Amalgam Trials).

just two as in the parent study) revealed a dose-related association between amalgam and certain porphyrins,[165] which are biomarkers for mercury-related enzyme damage.[166] The authors conclude:

> *"[The results] suggest that dental amalgams for the average individual do not cause a significant acute exposure to Hg, but instead represent* ***a significant life-long source of chronic exposure to Hg, with a continuing impact on increasing Hg body-burden****. It is of theoretical concern from extrapolation of our results that over the course of a life-time of 70 years, the contribution to Hg body-burden from dental amalgams may eventually result in elevations in urinary porphyrins similar to those observed in individuals with diagnosed neurological conditions associated with Hg intoxication...."*[167] *(Emphasis added.)*

In 2012, the original team[168] reanalyzed the Portugal dataset using urinary mercury measurements as the exposure variable instead of the amalgam-or-no-amalgam variable used in the 2006 analysis. They also controlled for a gene called CPOX, which has been shown to affect susceptibility to mercury via its role in heme biosynthesis. Of the original 507 children, 330 were available for genetic typing.

Results showed clear, significant, dose-related neurobehavioral deficits for boys with the CPOX4 genetic variant, which affects 28% of the population.[169] The authors note, "These findings are the first to demonstrate genetic susceptibility to the adverse neurobehavioral effects of Hg exposure in children," and "the modifying effects of commonly expressed genetic variants on these associations are just beginning to be defined."[170]

In 2012, others found amalgam-related biomarkers for kidney damage in the same genetically susceptible group.[171] As an aside, the recent findings linking amalgam with adverse health effects are foreshadowed in several earlier publications:

- An editorial accompanying the original 2006 publication of the two Children's Amalgam Trials warned against concluding that amalgam is safe;[172]
- A 2007 analysis found hints that excretion may become impaired over time;[173]
- A 2008 analysis found hints of kidney damage;[174] and
- A 2009 analysis found incipient changes in urinary porphyrins, suggesting toxicity.[175]

[165] Geier DA, Carmody T, Kern JK, King PG, Geier MR. A significant relationship between mercury exposure from dental amalgams and urinary porphyrins: a further assessment of the Casa Pia children's dental amalgam trial. Biometals. 2011;24(2):215–224. http://www.ncbi.nlm.nih.gov/pubmed/21053054

[166] Woods JS. Altered porphyrin metabolism as a biomarker of mercury exposure and toxicity. Can. J. Physiol. Pharmacol. 1996;74(2):210–215. http://www.ncbi.nlm.nih.gov/pubmed?term=PMID%3A%20%20%20%20%208723034

[167] Geier 2011, *op. cit.*

[168] The 2012 team included four of the original authors of the 2006 publication.

[169] Woods JS, Heyer NJ, Echeverria D, et al. Modification of neurobehavioral effects of mercury by a genetic polymorphism of coproporphyrinogen oxidase in children. Neurotoxicology and teratology. 2012. http://www.ncbi.nlm.nih.gov/pubmed?term=PMID%3A%20%20%20%20%2022765978

[170] *Ibid*.

[171] Geier D, Carmody T, Kern J, King P, Geier M. A significant dose-dependent relationship between mercury exposure from dental amalgams and kidney integrity biomarkers: A further assessment of the Casa Pia children's dental amalgam trial. Hum Exp Toxicol. 2012. http://www.ncbi.nlm.nih.gov/pubmed?term=PMID%3A%20%20%20%20%2022893351

[172] Needleman HL. Mercury in dental amalgam--a neurotoxic risk? JAMA. 2006 Apr 19;295(15):1835–6.

[173] Woods JS, Martin MD, Leroux BG, et al. The contribution of dental amalgam to urinary mercury excretion in children. Environ. Health Perspect. 2007;115(10):1527–1531. http://www.ncbi.nlm.nih.gov/pubmed?term=17938746

[174] Barregard L, Trachtenberg F, McKinlay S. Renal Effects of Dental Amalgam in Children: The New England Children's Amalgam Trial. Environ Health Perspect. 2008;116(3):394–399. http://www.ncbi.nlm.nih.gov/pubmed?term=18335109

In conclusion, one of the two randomized, controlled, clinical trials that forms the cornerstone for the claim that amalgam is safe now shows harm, and several other published studies are consistent with this finding.

[175] Woods JS, Martin MD, Leroux BG, et al. Urinary porphyrin excretion in children with mercury amalgam treatment: findings from the Casa Pia Children's Dental Amalgam Trial. J. Toxicol. Environ. Health Part A. 2009;72(14):891–896. http://www.ncbi.nlm.nih.gov/pubmed?term=19557617

Science versus policy

Science -- the pursuit of reliable knowledge -- requires a high level of certainty. Public policy on the other hand, involves balancing risks and benefits amidst ongoing uncertainty. Policymakers, unlike scientists, incur consequences for failing to act.

Scientists are averse to making statistical Type I errors (errors of commission; *i.e.,* accepting spurious relationships as true), but don't mind making Type II errors (errors of omission; *i.e.,* dismissing true relationships as spurious).[176] Thus, a large gray area exists in which associations may be *more* likely than not, yet do not meet an adequately high level of certainty. A 1987 editorial in the New England Journal of Medicine opines:

> *Science is a hard taskmaster, and in the light of mounting evidence that suggestions of toxicity are for the most part ultimately confirmed by painstaking inquiry, perhaps it is time to reexamine whether scientific standards of proof of causality -- and waiting for the bodies to fall -- ought not to give way to more preventative health policies that are satisfied by more realistic conventions and that lead to action sooner.*[177]

Pioneering epidemiologist Sir Austin Bradford Hill warned against applying statistical tests of significance too rigorously.[178] He argued that statistics is merely a tool to facilitate the goal of attaining scientific common sense, rather than a threshold to determine which studies are of value;[179] and he urged consideration of costs and benefits when heath is an issue.[180]

Sir John Lawton, scientist and former chair of the UK environmental commission, offered advice on how scientists can undertake advocacy, in a 2012 radio interview, saying, "Be true to the uncertainties."[181]

[176] Needleman H. Current status of childhood lead exposure at low dose. In: Chang LW, ed. Toxicology of metals. Boca Raton: Lewis Publishers; 1996, p 412.

[177] Ashford NA. New scientific evidence and public health imperatives. N. Engl. J. Med. 1987;316(17):1084–1085. http://www.ncbi.nlm.nih.gov/pubmed?term=3561461

[178] Hill AB. The environment and disease: Association or causation? Proc. R. Soc. Med. 1965;58:295–300. http://www.ncbi.nlm.nih.gov/pubmed/14283879

[179] Phillips CV, Goodman KJ. Causal criteria and counterfactuals; nothing more (or less) than scientific common sense. Emerg Themes Epidemiol. 2006;3:5. http://www.ncbi.nlm.nih.gov/pubmed?term=16725053

[180] Phillips CV, Goodman KJ. The missed lessons of Sir Austin Bradford Hill. Epidemiol Perspect Innov. 2004;1(1):3. http://www.ncbi.nlm.nih.gov/pubmed?term=15507128

[181] BBC radio. The life scientific. March 2012. http://www.bbc.co.uk/programmes/b01d0rtj Also described at http://www.carbonbrief.org/blog/2012/03/john-lawton-on-science-advocacy

FDA science and law

Wide use of amalgam pre-dates the establishment of the US Food and Drug Administration (FDA). In 1976, the Medical Device Amendments to the federal Food, Drug, and Cosmetics Act brought amalgam under FDA authority. The FDA's current position, promulgated in its 2009 amalgam rule,[182,183] is:

> FDA has reviewed the best available scientific evidence to determine whether the low levels of mercury vapor associated with dental amalgam fillings are a cause for concern. Based on this evidence, FDA **considers dental amalgam fillings safe for adults and children ages 6 and above**. The amount of mercury measured in the bodies of people with dental amalgam fillings is well below levels associated with adverse health effects. Even in adults and children ages 6 and above who have fifteen or more amalgam surfaces, mercury exposure due to dental amalgam fillings has been found to be far below the lowest levels associated with harm. Clinical studies in adults and children ages 6 and above have also found no link between dental amalgam fillings and health problems.[184] (Emphasis added.)

The FDA disregarded Congress's directive

The 1976 Amendments directed the FDA to assess the safety of medical and dental devices.[185] Three classes were established: Class I is generally recognized as safe; Class II is of moderate risk; and Class III requires proof of safety from manufacturers.[186] Yet the FDA classified amalgam first in Class I, then in Class II, not in Class III; thus proof of safety has never been required.

Congress mandated that devices should be classified as Class III, thus requiring premarket approval of safety, when insufficient information exists to provide reasonable assurance of safety:

> *(C)* ***Class III, Premarket Approval****.— A device which because —*
>
> *(i) it*
> *(I) cannot be classified as a class I device because insufficient information exists to determine that the application of general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device, and*
> *(II) cannot be classified as a class II device because insufficient information exists to determine that the special controls described in subparagraph (B) would provide reasonable assurance of its safety and effectiveness, and*
>
> *(ii)*
> *(I) is purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, or*
> *(II) presents a potential unreasonable risk of illness or injury,*
>
> *is to be subject, in accordance with section 360e of this title, to premarket approval to provide reasonable assurance of its safety and effectiveness.*[187]

Further, Congress mandated that implants be categorically placed in Class III:

> *(c) In the case of a device which has been referred under paragraph (1) to a panel, and which —*
>
> *(i) is intended to be* ***implanted in the human body*** *or is purported or represented to be for a use in supporting or sustaining human life, and*
> *(ii)(I) has been introduced or delivered for introduction into interstate commerce*

[182] US Food and Drug Administration, About Dental Amalgam Fillings, Appendix I: Summary of Changes to the Classification of Dental Amalgam and Mercury, 2009. www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DentalProducts/DentalAmalgam/ucm171120.htm

[183] US Food and Drug Administration. Final rule for dental amalgam. 21 CFR Part 872. July 28, 2009, published August 4, 2009. http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/DentalProducts/DentalAmalgam/UCM174024.pdf

[184] FDA website: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DentalProducts/DentalAmalgam/ucm171094.htm

[185] Wizemann T. Legislative History of the Medical Device Amendments of 1976. In: Public Health Effectiveness of the FDA 510(k) Clearance Process: Balancing Patient Safety and Innovation: Workshop Report. Washington, DC: National Academies Press. 2010. http://www.nap.edu/openbook.php?recaord_id=12960&page=3

[186] FDA website. http://www.fda.gov/medicaldevices/productsandmedicalprocedures/deviceapprovalsandclearances/pmaapprovals/default.htm

[187] 21 U.S.C. §§360a, *et seq.*

for commercial distribution before May 28, 1976, or

(iii) is within a type of device which was so introduced or delivered before such date and is substantially equivalent to another device within that type,

such panel shall recommend to the Secretary that the device be classified in class III unless the panel determines that classification of the device in such class is not necessary to provide reasonable assurance of its safety and effectiveness. If a panel does not recommend that such a device be classified in class III, it shall in its recommendation to the Secretary for the classification of the device set forth the reasons for not recommending classification of the device in such class.[188] *(Emphasis added.)*

Further, FDA rules state:

Although no device can be regulated adequately in Class I or Class II unless there are adequate data and information establishing its safety and effectiveness, a device for which there are such data and information may nevertheless require regulation in Class III because of the public health concerns posed by its use."[189]

The FDA's amalgam rule is based on optimistic assumptions

The FDA assumes an average exposure from amalgam of 5 micrograms per day but fails to address the large variability documented among individuals in terms of both exposure and susceptibility. It uses outdated LOAEL studies and uncertainty factors used by EPA in 1995 and ATSDR in 1999, rather than the more current data used by CalEPA and others.[190] In its own words, the FDA has little or no margin of safety:

FDA has found that scientific studies using the most reliable methods have shown that dental amalgam exposes adults to amounts of elemental mercury vapor below ***or approximately equivalent to the protective levels of exposure identified by ATSDR and EPA****. (Emphasis added.).*[191]

According to Chang's *Toxicology of Metals* (1996):

[T[he absence of a substantial safety margin is clearly worrisome, especially as dose-response relationships obtained from occupationally exposed groups are likely to underestimate the risks in the whole population. The level of exposure to mercury vapor where significant toxic effects may occur is not well established, but it appears that the safety margin for cases of maximum exposure to mercury from amalgam fillings is not satisfactory.[192]

The FDA disregarded its 2006 science advisory panel

In 2006, the FDA's science advisory panel discredited the FDA's amalgam rule and its underlying criteria document known as the White Paper.[193] Specifically, the panel was asked whether the White Paper "objectively and clearly presented the current state of knowledge about the exposure and health effects related to dental amalgam." The panel of dentists and scientists voted "no" by a 13-7 margin. To the question of whether the White Paper's conclusions were "reasonable," the panel also voted "no" by the same 13-7 margin.[194] According to the 2006

[188] 21 U.S.C. §§360c, *et seq.*

[189] 42 FR 46030, [13 Sep 1977]

[190] Lettmeier 2010, *op. cit.*

[191] US Food and Drug Administration, About Dental Amalgam Fillings, Appendix I: Summary of Changes to the Classification of Dental Amalgam and Mercury, 2009. www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DentalProducts/DentalAmalgam/ucm171120.htm.

[192] Weiner 1996, *op. cit.*

[193] FDA CHRH 2006 meeting documents: http://www.fda.gov/ohrms/dockets/ac/cdrh06.html For meeting minutes and transcripts, see Dental Products Panel: September 6 and 7, 2006 with Peripheral & Central Nervous System Drugs Advisory Committee.

[194] The 2006 panel took two votes addressing the questions, "Does the FDA draft White Paper objectively and clearly present the current state of knowledge about the exposure and health effects related to dental amalgam?" and "Given

meeting summary, “Those voting no expressed concern that the paper contained too many research gaps and implied a safety that was not really known. Those voting yes recognized deficiencies but felt the conclusions were reasonable for the available data.”[195]

In 2009, the FDA issued a “final” amalgam rule with no significant changes to its previous rule.[196] Technically, the rule designates amalgam as Class II (moderate risk), but it imposes no notable restrictions, aside from some labeling requirements for dentists (not patients). Ironically, the summary of the 2009 rule mentions, “two clinical trials in children aged six and older did not find neurological or renal injury associated with amalgam use,” referring to the two Children’s Amalgam Trials, one of which as of 2012 finds several types of harm. (See p.22.)

The FDA disregarded its 2010 science advisory panel

Citizens groups petitioned the FDA to reconsider the 2009 final rule, and in response, the FDA held a public meeting and convened a science advisory panel in December 2010. This time, the FDA avoided asking the panel to judge its rule or its underlying analysis, but instead pursued ten, limited, technical questions. Nonetheless, several panel members offered the unsolicited comment that amalgam should be banned in pregnant women and children. The gist of the panel’s discussion was that there is an absence of scientific data to support the FDA’s conclusion that amalgam is safe.[197] Specific concerns of the panel included: the use of average exposures instead of a distribution of a range of exposures; the lack of data on human developmental effects in the face of *in vitro* and animal evidence of harm; the limitations of using urinary mercury levels within studies; the lack of data on bioaccumulation and clearance; the need to consider sensitive subpopulations; and the lack of data on the role of mercury in neurodegenerative diseases.[198]

The FDA has failed to implement any protections to limit the harm from amalgam

In Chang’s *Toxicology of Metals* (1996), the authors of a review on amalgam opine that mercury should be regulated as a pharmaceutical device, with appropriate pre-market testing and post-market safety evaluation.[199]

Others advocate amalgam performance standards to minimize mercury release.

the amount and quality of information available for the draft FDA White Paper, are the conclusions reasonable?”

[195] US Food and Drug Administration, Summary Minutes, Joint Meeting of the Dental Products Panel and Peripheral and Central Nervous System Drugs Advisory Committee, Sept. 7, 2006. http://www.fda.gov/ohrms/dockets/ac/06/minutes/2006-4218m2.pdf

[196] US Food and Drug Administration, About Dental Amalgam Fillings, Appendix I: Summary of Changes to the Classification of Dental Amalgam and Mercury, 2009 On-line: www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DentalProducts/DentalAmalgam/ucm171120.htm

[197] FDA Advisory Committees: 2010 Meeting Materials of the Dental Products Panel. http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/DentalProductsPanel/ucm235085.htm See meeting transcripts and 24-hour summary.

[198] US Food and Drug Administration, December 15, 2010: Meeting Transcript, 2010 Meeting Materials of the Dental Products Panel, FDA Generated, Gaithersburg, MD, December 14-15, 2010. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/DentalProductsPanel/UCM242363.pdf

[199] Weiner 1996, *op. cit.*

Lack of informed consent

The public warnings provided by the FDA and the California Dental Association fail to covey accurately the potential risks of dental amalgam. Both acknowledge a controversy but bury its significance amidst a sea of trivial information. Once merely biased, the information is now incorrect.

The FDA website as of 2012 states, within the fine print:[200]

> *Dental amalgam contains elemental mercury. It releases low levels of mercury vapor that can be inhaled. High levels of mercury vapor exposure are associated with adverse effects in the brain and the kidneys.*
>
> *FDA has reviewed the best available scientific evidence to determine whether the low levels of mercury vapor associated with dental amalgam fillings are a cause for concern. Based on this evidence, FDA considers dental amalgam fillings safe for adults and children ages 6 and above.* ***[Left unstated is the important fact that amalgam may be unsafe for pregnant women and young children.].*** *The amount of mercury measured in the bodies of people with dental amalgam fillings is well below levels associated with adverse health effects.* ***[This generalization is unsupportable.]*** *Even in adults and children ages 6 and above who have fifteen or more amalgam surfaces, mercury exposure due to dental amalgam fillings has been found to be far below the lowest levels associated with harm.* ***[This statement is not universally true. Further, the "levels associated with harm" are taken from occupational studies of healthy adults, presumably without genetic susceptibilities or other compromised health.]*** *Clinical studies in adults and children ages 6 and above have also found no link between dental amalgam fillings and health problems.* ***[This is no longer true; the Portugal Children's Amalgam Trial reveals three types of harm to children.]***
>
> *There is limited clinical information about the potential effects of dental amalgam fillings on pregnant women and their developing fetuses, and on children under the age of 6, including breastfed infants. However, the estimated amount of mercury in breast milk attributable to dental amalgam is low and falls well below general levels for oral intake that the Environmental Protection Agency (EPA) considers safe.* ***[Th EPA has not yet considered developmental toxicities when setting standards. The CalEPA has, and set a standard ten times lower than the EPA, meaning that breast milk from amalgam-bearing mothers may be a developmental toxin.]*** *FDA concludes that the existing data support a finding that infants are not at risk for adverse health effects from the breast milk of women exposed to mercury vapor from dental amalgam. The estimated daily dose of mercury vapor in children under age 6 with dental amalgams is also expected to be at or below levels that the EPA and the Centers for Disease Control and Prevention (CDC) consider safe.* ***[But not CalEPA].*** *Pregnant or nursing mothers and parents with young children should talk with their dentists if they have concerns about dental amalgam.* ***[Dentists are not necessarily forthcoming about such risks.]***
>
> *Some individuals have an allergy or sensitivity to mercury or the other components of dental amalgam (such as silver, copper, or tin). Dental amalgam might cause these individuals to develop oral lesions or other contact reactions. If you are allergic to any of the metals in dental amalgam, you should not get amalgam fillings.* ***[The risk of allergy should not be used to distract from the risk of toxicity.]*** *You can discuss other treatment options with your dentist.*

Similarly, the 2004 California Dental Association brochure, The Facts about Fillings, states,[201]

> *[The mercury content of amalgam] has caused discussion about the risks of mercury in dental amalgam. Such mercury is emitted in minute amounts as vapor. Some concerns have been raised regarding possible toxicity. Scientific research continues on the safety of dental amalgam. According to the Centers for Disease Control and Prevention, there is scant evidence that the health of the vast majority of people with amalgam is compromised.* ***[Left unstated are the risks to vulnerable subpopulations.]***
>
> *The Food and Drug Administration (FDA) and other public health organizations have investigated the safety of amalgam used in dental fillings. The conclusion: no valid scientific evidence has shown that amalgams cause harm to patients with dental restorations, except in rare cases of allergy. The World Health Organization reached a*

[200] US Food and Drug Administration, About dental amalgam fillings (2012) (available at http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DentalProducts/DentalAmalgam/ucm171094.htm).

[201] California Dental Board, The facts about filings (2004) (available at http://www.dbc.ca.gov/formspubs/pub_dmfs2004.pdf).

> *similar conclusion stating, "Amalgam restorations are safe and cost effective."* ***[This is no longer an accurate presentation of the WHO position.]***
>
> *A diversity of opinions exists regarding the safety of dental amalgams. Questions have been raised about its safety in pregnant women, children, and diabetics. However, scientific evidence and research literature in peer-reviewed scientific journals suggest that otherwise healthy women, children, and diabetics are not at an increased risk from dental amalgams in their mouths.* ***[This is untrue.]*** *The FDA places no restrictions on the use of dental amalgam.*

A 2006 Zogby poll found that only 40% of Californians know that mercury is the primary component of dental amalgam.[202] Even when this fact is disclosed as in the official language above, the lack of focus on toxic risks is misleading at best. Reasonable patients naively believe that health authorities are protecting the public from risks when feasible, therefore, dental amalgam is safe. Patients are unlikely to perceive the unstated risks in the above disclosures, or to scrutinize fine print. A skull-and-crossbones image may convey the concept quickly.

Relying on dentists to convey information would be naive, given the historical record. Patients frequently receive misinformation from dentists and doctors.[203] What recourse will consumers have for such misinformation? How will those with existing amalgams learn of the health risks? Since mercury is most toxic to the developing fetus, how can any reasonable public policy not restrict placement of amalgam in pregnant women?

Whatever the informed-consent resolution, it may be unenforced and unenforceable, as in Philadelphia,[204] which may reflect poorly on the local authorities.

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[202] 2006 Zogby poll http://www.toxicteeth.org/zogby-poll--results-2006.aspx

[203] Anecdotes of the Bay Area Chronic Mercury Poisoning Support Group, facilitated by the author.

[204] http://legislation.phila.gov/attachments/4696.pdf

Alternatives

A 2012 study found that the durability of properly placed composites is similar to that of amalgams.[205]

Three professional dental societies oppose the use of mercury dental amalgam:

- The International Academy of Oral Medicine and Toxicology;[206]
- The International Academy of Biological Dentistry and Medicine;[207] and
- The Holistic Dental Association.[208]

Many of their members have practiced dentistry for decades without the need for amalgam.

Yet amalgam is still used extensively. A 2011 study found that most posterior teeth needing restoration are filled with amalgam.[209] A 2005 survey found that 30% of dentists were amalgam free,[210] and an informal 2007 survey found that about half of all dentists were amalgam-free.[211]

[205] Heintze SD, Rousson V. 2012. Clinical Effectiveness of Direct Class II Restorations - A Meta-Analysis. J Adhes Dent. Oct; 14(5):407-31. http://www.ncbi.nlm.nih.gov/pubmed/23082310

[206] IAOMT website. http://iaomt.org/

[207] IABDM website. http://iabdm.org/

[208] HDA website. http://www.holisticdental.org/

[209] Makhija SK, Gordan VV, Gilbert GH, et al. Practitioner, patient and carious lesion characteristics associated with type of restorative material: findings from The Dental Practice-Based Research Network. J Am Dent Assoc. 2011;142(6):622–632. http://www.ncbi.nlm.nih.gov/pubmed?term=PMID%3A%20%20%20%2021628683

[210] Haj-Ali R, Walker MP, Williams K. Survey of general dentists regarding posterior restorations, selection criteria, and associated clinical problems. Gen Dent. 2005;53(5):369–375; quiz 376, 367–368. http://www.ncbi.nlm.nih.gov/pubmed/16252541

[211] The WealthyDentist.com http://thewealthydentist.com/surveyresults/16_mercuryamalgam_results.htm

Amalgam bans and restrictions, US and abroad

Even before the recent evidence of harm to children emerged (p. 22), a growing number of countries banned or restricted the use of mercury dental amalgam. In 2008 the governments of Norway, Sweden, and Denmark banned amalgam.[212] Norwegian officials cited risks to the environment, Swedes cited both health and environmental concerns, and Danes cited the availability of improved composites as an alternative.[213] Exceptions to use amalgam may be granted for a certain period after the ban, if dentists apply for it.[214]

In 1997, the German government and several German dental associations issued a consensus statement that amalgam placement or removal should be avoided in pregnant women.[215] In 1996, Health Canada issued a position statement on dental amalgam asserting that amalgam fillings should not be placed in or removed from pregnant women.[216]

France, Finland, and Austria have recommended that alternative dental materials be used for pregnant women.[217]

Within the US, in 2007, the city of Philadelphia, PA passed an ordinance requiring dentists to provide information to patients and to obtain informed consent before placing mercury dental amalgam.[218] The ordinance lacks an enforcement mechanism. In 2010, the city of Costa Mesa, CA passed a resolution opposing the use of mercury dental amalgam and requesting that all dental practices within the city voluntarily cease use of amalgam.[219] In 2011, the city of Malibu, CA passed a resolution supporting reduction of mercury use including efforts by the United Nations to phase out major uses of mercury including dental amalgam.[220]

[212] Dental Mercury Use Banned in Norway, Sweden and Denmark because Composites are Adequate Replacements," Reuters/PRNewswire-USNewswire Online. January 3, 2008. http://www.reuters.com/article/idUS108558+03-Jan-2008+PRN20080103

[213] *Ibid.*

[214] *Ibid.*

[215] Working Group on Dental Amalgam for the United States Department of Health and Human Services. Dental Amalgam and Restorative Materials: An Update Report to the Environmental Health Policy Committee. (Washington, D.C.: update report, October 1997), 4-6. http://web.health.gov/environment/amalgam2/contents.html.

[216] Health Canada. The Safety of Dental Amalgam. 1996. http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/md-im/dent_amalgam-eng.pdf

[217] Health and Environment Alliance. Mercury and Dental Amalgams. (Brussels, Belgium: fact sheet, May 2007): 3. http://www.env-health.org/IMG/pdf/HEA_009-07.pdf

[218] Philadelphia informed consent ordinance. December 13, 2007. http://legislation.phila.gov/attachments/4696.pdf

[219] A resolution of the city of Costa Mesa opposing the use of dental mercury. October 19, 2010. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/DentalProductsPanel/UCM236365.pdf

[220] Malibu resolution addressing major sources of anthropogenic mercury. October 10, 2011. http://www.malibucity.org/download/index.cfm/fuseaction/download/cid/17571/

Political context (incomplete)

The divide within dentistry

Political scandals within FDA

The ADA lobby

ADA gag rules

ADA disinformation campaigns

ADA origins

Amalgam is inert

Amalgam is like sodium chloride

Exposures are harmless

Adverse effects are due to allergy

Patients prefer composites for aesthetic reasons

“What Others Say”

Spinning the 2010 FDA hearing

ADA skirts legal liability

Framing the issue