AMALGAM RISK ASSESSMENT

Mercury from Dental Amalgam: Exposure and Risk Assessment

Stephen M. Koral, DMD, FIAOMT

Abstract: There has long been an undercurrent within the dental profession of anti-amalgam sentiment, a "mercury-free" movement. To assess whether anything is or is not scientifically wrong with amalgam, one must look to the vast literature on exposure, toxicology, and risk assessment of mercury. The subject of risk assessment goes straight to the heart of the debate over whether amalgam is safe, or not, for unrestricted use in dentistry in the population at large.

Dental amalgam has been used to restore teeth for nearly 200 years, and doubts about the apparent contradiction of providing a healthcare service with a material that contains mercury have persisted the entire time. There has long been an undercurrent of anti-amalgam sentiment within the dental profession—ie, a "mercury-free" movement. While expressions of that sentiment have grown in recent years as it becomes easier to accomplish good restorative dentistry with composites, dentists generally feel that there is nothing wrong with amalgam scientifically—it's just that they aren't using it as much now.

As more dentists choose to practice without amalgam,[1] and as it becomes easier to accomplish good restorative dentistry with composites,[2] the dental industry must bear in mind that there are open questions about resin safety, too.[3-5] Exposure to bisphenol-A and other possible endocrine disruptors from dental fillings still needs more investigation.

Responses to the question of whether there is, in fact, something scientifically wrong with amalgam can be found in the vast literature on exposure, toxicology, and risk assessment of mercury that lies mainly outside the sources of information to which dentists are commonly exposed. Even much of the literature on mercury exposure from amalgam exists outside of dental journals. An examination of this extended literature can shed some light on the assumptions that dentistry has made about amalgam safety, and can help explain why some dentists have persistently objected to the use of amalgam in restorative dentistry.

It is now indisputable that dental amalgam releases metallic mercury into its environment at some rate. This review briefly summarizes some of the evidence for that exposure. The toxicology of mercury is too broad a subject to be covered in this article but is thoroughly reviewed elsewhere.[6,7] The subject of risk assessment, however, goes straight to the heart of the debate over whether amalgam is safe or not for unrestricted use in the population at large.

Amalgam: An Inter-Metallic Colloid

Since it is a cold mixture, amalgam meets neither the definition of an alloy, which must be a mixture of metals formed in a molten state, nor an ionic compound like salt, which must have an exchange of electrons resulting in a lattice of charged ions. It best meets the definition of an inter-metallic colloid, or solid emulsion, in which the matrix material is not completely reacted and is recoverable. Figure 1 shows a micrograph of a polished metallurgical sample of dental amalgam that had been impressed by a microscopic probe. At each point of pressure, droplets of liquid mercury are expressed.

A study by Haley[8] measured in-vitro release of mercury from single-spill samples of Tytin® (Kerr Corporation, www.kerrdental.com), Dispersalloy® (DENTSPLY Caulk, www.caulk.com), and Valiant® (Ivoclar Vivadent Inc., www.ivoclarvivadent.us), each with a surface area of 1 cm^2. After 90 days storage to allow the initial setting reactions to be complete, the samples were placed in distilled water at room temperature, 23°C, and not agitated. The distilled water was changed and analyzed daily for 25 days, using a Nippon Direct Mercury Analyzer (Nippon Instruments North America, http://hg-nic.us). Mercury was released under these conditions at a rate of 4.5 µg to 22 µg per square centimeter per day. Chew[9] reported that mercury dissolved from amalgam into distilled water at 37°C at a rate of up to 43 µg per day, while Gross and Harrison[10] reported 37.5 µg per day in Ringer's solution.

Distribution of Mercury Around the Body

Numerous studies, including autopsy studies, have shown higher levels of mercury in the tissues of humans with amalgam fillings, as opposed to those who were not similarly exposed. Increasing amalgam

load is associated with increasing mercury concentration in: exhaled intraoral air; saliva; blood; feces; urine; various tissues including liver, kidney, pituitary gland, brain, etc.; amniotic fluid; umbilical cord blood; placenta; fetal tissues; colostrum; and breast milk.[11]

The most graphic, classic experiments showing in-vivo distribution of mercury from amalgam fillings were the well-known "sheep and monkey studies" of Hahn et al, which were published in 1989 and 1990.[12,13] A pregnant sheep was given 12 occlusal amalgam fillings that were tagged with radioactive ^{203}Hg, an isotope that does not exist in nature and has a half-life of 46 days. The fillings were carved out of occlusion, and the animal's mouth was kept packed and rinsed to prevent swallowing of excess material during the operation. After 30 days, it was sacrificed. Radioactive mercury was concentrated in the liver, kidneys, digestive tract, and jawbones, but every tissue—including the fetal tissues—received measurable exposure. The autoradiogram of the whole animal, after the teeth were removed, is shown in Figure 2.

After the sheep experiment was criticized for using an animal that ate and chewed in a way that is fundamentally different from humans, the group repeated the experiment using a monkey, with the same results.

Risk Assessment

Evidence of exposure is one thing, but if "the dose makes the poison," as is often said in regard to mercury exposure from dental amalgam, a determination of the level of exposure that is poisonous and for whom is the province of risk assessment. Risk assessment is a set of formal procedures that use data available in the scientific literature to propose levels of exposure that may be acceptable under given circumstances, to authorities responsible for risk management. It is a process commonly used in engineering, for example, by the public works department, which needs to know the probability that a bridge will fail under a load before setting a weight limit on it.

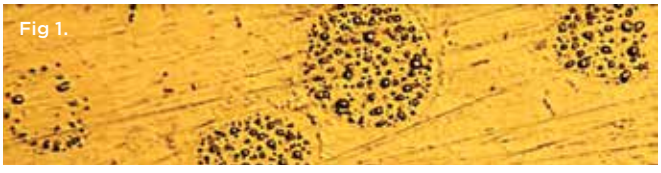
A number of agencies are responsible for regulating human exposure to toxic substances; they include US Food and Drug Administration (FDA), US Environmental Protection Agency (EPA), and Occupational Safety and Health Administration (OSHA). They all rely on risk assessment procedures to set acceptable residue limits for chemicals, including mercury, in fish and other foods, drinking water, and air. These agencies then set legally enforceable limits on human exposures, which are identified by a variety of terms, such as regulatory exposure limit (REL), reference dose (RfD), reference concentration (RfC), tolerable daily limit (TDL), etc.—all of which mean essentially the same thing: the amount of exposure to allow under the conditions for which the agency is responsible. This allowable level must be one at which there is an expectation of no negative health outcomes within the population covered under the regulation.

Establishing RELs

In order to apply risk assessment methods for possible mercury toxicity from dental amalgam, it is necessary to determine the dose of mercury that people are exposed to from their fillings, and compare that to established safety standards for that type of exposure. The toxicology of mercury recognizes that its effects on the body depend greatly on the chemical species involved and the route of exposure. Nearly all the work on amalgam toxicity assumes that the major toxic species involved is metallic mercury vapor (Hg^0) that is emitted by the fillings, inhaled into the lungs, and absorbed at a rate of 80%. Other species and routes are known to be involved, including metallic mercury dissolved in saliva, abraded particles, and corrosion products that are swallowed, or methyl mercury produced from Hg^0 by intestinal bacteria. Even more exotic identified pathways include absorption of Hg^0 into the brain through the olfactory epithelium or retrograde axonal transport of mercury from the jawbones into the brain. These exposures are either of unknown quantity or are assumed to be of much lesser magnitude than oral inhalation, so the great bulk of research on amalgam mercury has concentrated there.

The central nervous system (CNS) is presumed to be the most sensitive target organ for mercury vapor exposure.[14,15] Effects due to hypersensitivity, autoimmunity, and other allergic type mechanisms cannot be accounted for by dose-response models—bringing into question whether allergy to mercury actually is rare. Therefore, researchers and agencies seeking to establish RELs for low-level chronic Hg^0 exposure have looked at various measures of CNS effects. Scientists have relied upon a few key risk assessment studies (summarized in Table 1)[16-23] published over the years that connect the quantity of mercury vapor exposure with measurable signs of CNS dysfunction.

The practice of risk assessment recognizes that exposure and effect data collected for adult, overwhelmingly male, workers in occupational settings cannot be used in their raw form as indicating



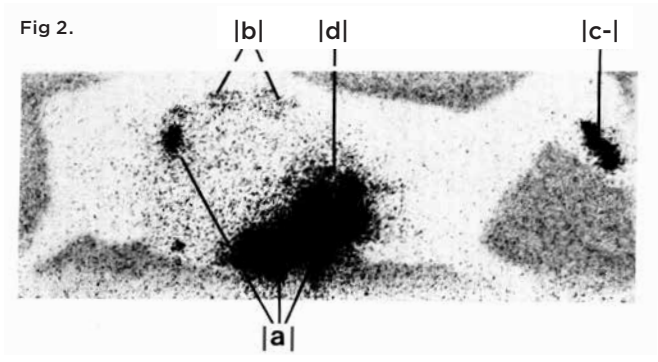


Fig 1. Micrograph of a polished metallurgical sample of dental amalgam that had been impressed by a microscopic probe. (Source: Masi JV. Corrosion of Restorative Materials: The Problem and the Promise. Symposium: Status Quo and Perspectives of Amalgam and Other Dental Materials, April 29-May 1, 1994.) **Fig 2.** Autoradiogram of sheep after teeth were removed, in experiment showing in-vivo distribution of mercury from amalgam fillings.

safe levels for everyone. Factors suggesting uncertainty about the data include:

- ***LOAEL vs. NOAEL***—None of the exposure data gathered in the key studies has been reported in a manner that displays a clear dose-response curve for the CNS effects measured. As such, they do not show a definite threshold dose for onset of the effects. In other words, there is no determination of a No-Observed-Adverse-Effect-Level (NOAEL). The studies each do point to a Lowest-Observed-Adverse-Effect-Level (LOAEL), which is not considered to be definitive.
- ***Human Variability***—There are many groups of more sensitive people in the general population, including: infants and children with more sensitive developing nervous systems and lower body weight; people with medical compromises; people with genetically determined increased sensitivity; women of childbearing age and other gender-related differences; and the elderly, to name a few. Interpersonal differences that are not accounted for in the data add to the uncertainty.
- ***Reproductive and Developmental Data***—Some agencies, such as the California EPA, place more emphasis on reproductive and developmental data, and plug an additional level of uncertainty into their calculations when it is lacking.
- ***Interspecies Data***—Applying animal research data to the human experience is never straightforward, but consideration of this factor does not apply in this instance, because the key studies cited here all involved human subjects.

Published RELs for chronic mercury vapor exposure in the general population are summarized in Table 2.[7,11,16,19,20,22,24-26] RELs meant to regulate exposure for the whole population are calculated to assure that there can be no reasonable expectation of adverse health effects for anyone, so allowable exposures are reduced from the observed lowest effect levels by arithmetic "uncertainty factors" (UF). Uncertainty factors are not decided by hard and fast rules, but by policy—the degree of caution the regulatory agency wants to exercise and its level of confidence in the data.

In the case of the US EPA, for example, the effect level (9 µg-Hg/cubic meter air) is reduced by a factor of 3 due to reliance on a LOAEL, and by a factor of 10 to account for human variability, for a total UF of 30. This results in an allowable limit of 0.3 µg-Hg/cubic meter air.[26]

The California EPA added an additional UF of 10 for lack of reproductive and developmental data for Hg^0, making their limit 10 times as strict, 0.03 µg Hg/cubic meter air.[25]

A study by Ngim et al[20] presented both male and female dentists in Singapore who were chronically exposed to low levels of mercury vapor without the presence of chlorine gas (Table 2). In a study published in 2009, Richardson et al[24] identified the Ngim study as the most appropriate basis for developing an REL and, therefore, used a UF of 10 rather than 3 for the LOAEL, arguing that infants and children are much more sensitive than a factor of 3 can account for. Applying a UF of 10 for human variability, for a total UF of 100, he recommended that Health Canada set their REL for chronic mercury vapor at 0.06 µg Hg/cubic meter air.[24]

TABLE 1

Key Studies Used to Calculate Reference Concentrations for Metallic Mercury Vapor, Expressed As Micrograms Per Cubic Meter of Air

Study	Subjects	Symptoms	LOAEL occupational exposure µg Hg/cubic meter air	Conversion for 168 hour week µg Hg/cubic meter air
Fawer[16] (1983)	26 male workers (12 chloralkali)	Tremor	26	9
Piikivi and Tolonen[17] (1989)	41 male chloralkali workers	EEG abnormalities	25*	9
Piikivi and Hänninen[18] (1989)	60 male chloralkali workers	Subjective psychological	25*	9
Piikivi[19] (1989)	41 male chloralkali workers	Autonomic dysfunction	30*	10.8
Ngim et al[20] (1992)	60 male dentists, 38 female dentists	Neurobehavioral	23*	9
Liang et al[21] (1993)	Fluorescent lamp workers: 69 male, 19 female	Neurobehavioral	25*	9
Lettmeier et al[22] (2010)	306 small-scale gold miners	Neurological, emotional	3.0*	

**Air concentrations derived by converting blood or urine values to an air equivalent according to conversion factors (from Roels et al[23]).*

Lettmeier et al[22] found highly statistically significant objective (ataxia of gait) and subjective (sadness) effects in small-scale gold miners in Africa, who use mercury to separate gold from crushed ore, at even lower exposure levels—3 µg Hg/cubic meter air. Following the US EPA, they applied a UF range of 30 to 50, and suggested a REL between 0.1 and 0.07 µg Hg/cubic meter air.

Problems with RELs

The US EPA last revised its mercury vapor REL (0.3 µg Hg/cubic meter air) in 1995, and although it reaffirmed the REL in 2007, EPA acknowledges that newer papers have been published that could convince it to revise the REL downward. The older papers of Fawer et al[16] and Piikivi et al[17-19] depended in great part on measurements of mercury exposure and CNS effects in chloralkali workers. Chloralkali is a 19th century chemical industry process in which salt brine is floated over a thin layer of liquid mercury and hydrolyzed with electrical current to produce sodium hypochlorite, sodium hydroxide, sodium chlorate, chlorine gas, and other products. The mercury acts as one of the electrodes. Workers in such plants are exposed not only to mercury in the air, but also chlorine gas as well.

As discussed and reviewed by Richardson et al,[24] concomitant exposure of mercury vapor and chlorine gas changes the dynamics of human exposure. The Hg^0 is partially oxidized by chlorine in the air to Hg^{2+}, or $HgCl_2$, which reduces its permeability in the lungs and dramatically alters its distribution in the body. In particular, $HgCl_2$ absorbed from air through the lungs does not get into cells, or through the blood-brain barrier, as easily as Hg^0. For example, Suzuki et al[27] showed that workers exposed to Hg^0 alone had a ratio of Hg in red blood cells to plasma of 1.5-2.0 to 1, while chloralkali workers exposed to both mercury and chlorine had a ratio of Hg in RBCs to plasma of 0.02 to 1, roughly 100 times less inside the cells. This phenomenon would cause the mercury to partition far more to the kidneys than the brain. The exposure indicator, urine mercury, would be the same for both types of workers, but the chloralkali workers would have much less CNS effect. By examining mostly chloralkali worker subjects, the sensitivity of the CNS to mercury exposure would be underestimated, and RELs based on these studies would be overestimated.

Among the newer papers is the work of Echeverria et al,[28] who finds significant neurobehavioral and neuropsychological effects in dentists and staff, well below the 25 µg Hg/cubic meter air level, using well-established standardized tests. Again, no threshold was detected.

Applying Mercury RELs to Amalgam

There is disparity in the literature concerning dosage of mercury exposure from amalgam, but there is broad consensus on some of the numbers involved, which are summarized in Table 3.[11,23,29,30] It helps to keep these basic figures in mind, as all the authors use them in their calculations. It also helps to keep in mind the fact that these exposure data are only analogs of exposure to the brain. There is animal data and post-mortem human data, but none on

TABLE 2

Published RELs for Exposure to Low-Level, Chronic Hg^0 Vapor in the General Population, Without Occupational Exposure

Published REL	Key Study	LOAEL µg Hg/ cubic meter air	Uncertainty Factors	REL µg Hg/ cubic meter air	REL, as absorbed dose µg Hg/kg-day*
Lettmeier et al[22]	Lettmeier et al[22]	3	30	0.07 to 0.1	0.011 to 0.016
Richardson et al[24] (2009)	Ngim[20]	6	100	0.06	0.01
Cal EPA (2005)[25]	Fawer[16], Piikivi[19], etc.	9	300	0.03	0.005
ATSDR[7] (1999)	Fawer[16]	6	30	0.2	0.032
US EPA[26] (1995)	Fawer[16], Piikivi[19], etc.	9	30	0.3	0.048

** Conversion to absorbed dose, µg Hg/kg-day, from Richardson et al[11] (2011).*

TABLE 3

Generally Agreed Upon Numbers for Amalgam and Mercury Exposure

Mean per surface release of Hg	0.4 µg/day [a] - 0.73 µg/day [b]	
Hg in urine per amalgam surface [c]	0.06-0.08 µg-Hg/g creatinine for adults	0.08-0.09 µg-Hg/g creatinine for children
Ratios of air: blood: urine [d]	1 µg-Hg/m^3 air ≅ 4.5 µg-Hg/L blood ≅ 1.22 µg-Hg/g creatinine	

[a] Mackert and Berglund (1997)[29] [b] Skare and Engkvist (1994)[30] [c] reviewed in Richardson et al (2011)[11] [d] Roels et al (1987)[23]

the actual movement of mercury into the brains of the workers involved in these studies.

The mid-1990s saw the publication of two divergent assessments of amalgam exposure and safety. The one that has had the most influence on discussions within the dental community was authored in 1997 by H. Rodway Mackert and Anders Berglund,[29] dental professors at the Medical College of Georgia and Umea University in Sweden, respectively. This is the paper in which the claim is made that it would take up to 450 surfaces of amalgam to approach a toxic dose. These authors cited papers that tended to discount the effect of chlorine on absorption of atmospheric mercury, and they used the occupational exposure limit, calculated for adult males exposed 8 hours per day, 5 days per week, of 25 µg-Hg/cubic meter air as their de-facto REL. They did not consider the uncertainty in that number, as it would apply to the whole population, including children, who would be exposed 24 hours, 7 days a week.

The calculation goes as follows: The lowest observed effect level for intentional tremor among adult male workers, primarily chloralkali workers, was 25 µg-Hg/cubic meter air, equating to a urine level of about 30 µg-Hg/gr-creatinine. Accounting for a small level of baseline urine mercury found in people without fillings, and dividing the 30 µg by the per-surface contribution to urine mercury, 0.06 µg-Hg/ gr-creatinine, the result is about 450 surfaces needed to reach that level.

Meanwhile, G. Mark Richardson, a risk assessment specialist employed by Health Canada, and Margaret Allan, a consulting engineer, both having no prior familiarity with dentistry, were tasked by that agency to perform a risk assessment for amalgam in 1995. They came to a very different conclusion than Mackert and Berglund. Using exposure-effect data and uncertainty factors in line with those discussed above, they proposed for Canada a REL for mercury vapor of 0.014 µg Hg/kg-day. Assuming 2.5 surfaces per filling, they calculated a range for the number of fillings that would not exceed that level of exposure for five different age groups, based upon body weight: toddlers, 0-1; children, 0-1; teens, 1-3; adults, 2-4; seniors, 2-4.[31,32]

In 2009, the US Food and Drug Administration, under pressure from a citizens' lawsuit, completed its classification of precapsulated dental amalgam, a process originally mandated by Congress in 1976.[33] They classified amalgam as a Class II device with certain labeling controls, meaning that they found it safe for unrestricted use for everyone. The labeling controls were meant to remind dentists that they would be handling a device that contains mercury, but there was no mandate to pass that information on to patients.

The FDA classification document was a detailed 120-page paper whose arguments depended largely on risk assessment comparing amalgam mercury exposure to the EPA's 0.3 µg-Hg/cubic meter air standard. However, the FDA analysis employed only the mean of the US population exposure to amalgam, not the full range, and, remarkably, did not correct for dose per body weight. It treated children as if they were adults. These points were forcefully contested in several "petitions to reconsider" submitted by both citizens' and professional groups to the FDA after publication of the classification. The petitions were considered cogent enough by FDA officials that the agency took the rare step of convening an expert panel to reconsider the facts of its risk assessment.

Richardson, now an independent consultant, was asked by several of the petitioners to update his original risk assessment. The new analysis, using detailed data on the number of filled teeth in the US population, was the center of discussion at the FDA's December 2010 expert panel conference. (See Richardson et al, 2011.[11])

Data on the number of filled teeth in the American population came from the National Health and Nutrition Examination Survey, a nationwide survey of about 12,000 people age 24 months and up. The collection of detailed dental health data was last completed in 2001-2004 by the National Center for Health Statistics, a division of the Centers for Disease Control and Prevention. It is a statistically valid survey representing the entire US population.

The survey collected data on the number of filled tooth surfaces, but not on the filling material. To correct for this deficiency, Richardson's group posited three scenarios, all suggested by extant literature: 1) all filled surfaces were amalgam; 2) 50% of filled surfaces were amalgam; 3) 30% of subjects had no amalgam; and 50% of the rest were amalgam. Under scenario 3, which assumes the fewest amalgam fillings, the calculated means of actual daily mercury dosage were:

- Toddlers: 0.06 µg-Hg/kg-day
- Children: 0.04 µg-Hg/kg-day
- Adolescents: 0.04 µg-Hg/kg-day
- Adults: 0.06 µg-Hg/kg-day
- Seniors: 0.07 µg-Hg/kg-day

All of these daily absorbed dose levels meet or exceed the daily absorbed dose of Hg^0 associated with published RELs, as seen in Table 2.

The number of amalgam surfaces that would not exceed the US EPA's REL of 0.048 µg-Hg/kg-day was calculated for toddlers, children, and young teens to be six surfaces. For older teens, adults, and seniors, it is eight surfaces. To not exceed the California EPA's REL, those numbers would be 0.6 and 0.8 surfaces.

However, these average exposures do not tell the whole story, and they do not indicate how many people exceed a "safe" dose. Examining the entire range of numbers of filled teeth in the population, Richardson calculated that there would currently be 67 million Americans whose amalgam mercury exposure exceeds the REL enforced by the US EPA. If the stricter California REL were applied, that number would be 122 million. This contrasts with the FDA's 2009 analysis, which considers only the mean number of filled teeth, and excludes persons less than 6 years of age, thus allowing the population exposure to just fit under the current EPA REL.

For amplification of this point, Richardson identified 17 papers in the literature that presented estimates of the dosage range of mercury exposure from amalgam fillings.[34] Comparing and contrasting those exposure estimates to the dose equivalents of the California EPA's REL, the strictest of the published regulatory limits for mercury vapor exposure, or to the US EPA's REL, the most lenient, indicates that most investigators whose papers were

presented would conclude that unrestricted use of amalgam would result in overexposure to mercury.

The Future of Amalgan

As of November 2012, the FDA had not announced a response to the petitions to reconsider the regulatory status of dental amalgam. It is hard to see how the agency will be able to give amalgam a green light for unrestricted use. It is clear that unrestricted use can expose people to mercury in excess of the EPA's REL, the same limit to which the coal-fired power industry is being forced to spend billions of dollars to comply. The EPA estimates that as of 2016, lowering emissions of mercury, along with soot and acid gases, would save $59 billion to $140 billion in annual health costs, preventing 17,000 premature deaths a year along with illnesses and lost workdays. Moreover, the contrast between the Mackert and Berglund approach to amalgam safety and that of Richardson highlights the polarization that has characterized the historic "amalgam wars." Either we say "it can't hurt anyone," or "it's bound to hurt someone." In this age of good resin-based restorative dentistry, when increasing numbers of dentists are practicing entirely without amalgam, dentists have the opportunity to be precautionary.

ABOUT THE AUTHOR

Stephen M. Koral, DMD, FIAOMT
Private Practice, Boulder, Colorado

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