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October 10, 2012

VIA EMAIL— *Sanco-SCENIHR-Secretariat@ec.europa.eu*

Scientific Committee on Emerging
and Newly Identified Health Risks

Re: Dental Amalgam—Call for Information

To Whom it May Concern:

Following is the Position Statement on Dental Amalgam from the International Academy of Oral Medicine and Toxicology ("IAOMT") submitted in response to the "Call for Information" extended by the Scientific Committee on Emerging and Newly identified Health Risks ("SCENIHR"). We attach to this email some of the publications that are referenced in this document. Attaching all, or even a substantial portion, of these publications to one email would cause its delivery to be rejected. We will therefore be attaching publications to a series of emails that will clearly identify the sender as the IAOMT. We hope this is acceptable.

Unfortunately, we are not currently in possession of all of the publications cited in the Position Statement. Given the time constraints imposed by SCENIHR, it was not possible to locate and send all of these documents. Nevertheless, most of the publications are in our possession and will be forwarded as attachments to a series of emails. Given additional time, we are confident that we can locate and forward all of the cited publications. In any event, we believe that the most important publications are in our possession and are currently available to be forwarded.

Please contact us if you have any questions concerning the IAOMT Position Statement.

Sincerely yours,

Kym Smith

Kym Smith, Executive Director

POSITION STATEMENT ON DENTAL AMALGAM FROM THE INTERNATIONAL ACADEMY OF ORAL MEDICINE AND TOXICOLOGY SUBMITTED IN RESPONSE TO THE "CALL FOR INFORMATION" EXTENDED BY THE SCIENTIFIC COMMITTEE ON EMERGING AND NEWLY IDENTIFIED HEALTH RISKS ("SCENIHR")

I. Introduction

The International Academy of Oral Medicine and Toxicology ("IAOMT") submits this position statement in response to the "Call for Information" extended by SCENIHR. The IAOMT is a non-profit corporation organized under the laws of the State of Oklahoma. Its principal place of business is in Kissimmee, Florida, USA. The IAOMT is a twenty-seven-year-old organization of dentists, physicians, and research professionals devoted to the examination, compilation, and dissemination of scientific research relating to the biocompatibility of oral/dental materials. The fundamental mission of the International Academy of Oral Medicine and Toxicology is to promote the health of the public. In this regard, the IAOMT continually examines and compiles scientific research relating to the biocompatibility of oral/dental materials. It also:

- Accumulates and disseminates scientific information;
- Promotes relevant research and education;
- Promotes funding for relevant research;
- Promotes education of the public, professional organizations, and other groups, by providing scientific information;
- Promotes non-invasive scientifically sound therapies;
- Provides advisory services if/when required;
- Promotes mercury-free dentistry.

After thoroughly reviewing the available scientific literature, the membership of the IAOMT is decidedly opposed to the use of mercury in dentistry. Mercury is a constituent of dental amalgam, a restorative material commonly used in dentistry. Based on its review of the peer-reviewed scientific literature, the IAOMT has petitioned the governments of the world to eliminate, or at least restrict, the use of mercury in dentistry. The IAOMT promotes mercury-free dentistry, and seeks to raise the standards of scientific biocompatibility in dental practice.

II. Summary of the IAOMT Position on the Use of Dental Amalgam

The IAOMT seeks a ban on the use of encapsulated mercury fillings as a dental restorative material. The risk of illness or injury associated with the use of dental mercury presents an unreasonable, direct and substantial danger to the health of dental patients as well as dental personnel. Mercury fillings potentially endanger the health of individuals who have been or will be exposed to dental mercury. The weight of the published scientific evidence decidedly supports the position of the IAOMT.

III. Previous Experience and Activities

In July 2008, the IAOMT sponsored a Citizen's Petition with the U.S. Food & Drug Administration ("FDA") demanding that FDA classify dental amalgam in conformance with the mandate of the Medical Device Amendments of 1976 (MDA), 21 U.S.C. 360c, *et seq*. On July 28, 2009, FDA announced that it was classifying dental amalgam for the first time in Class II without requiring any significant special controls. FDA's Final Rule on this issue was published on August 4, 2009. FDA also published an Addendum in support of its Final Rule, in which it attempts to address the recommendations of the Joint Panels that convened in September 2006. The Joint Panels rejected the proclamations of dental amalgam safety set forth in the FDA's White Paper on amalgam fillings. Following the issuance of the FDA's Final Rule, IAOMT sponsored a Petition for Reconsideration in which it identified at least seventeen errors committed by FDA in its discussion of risk assessment principles. Based on the IAOMT Petitions, FDA scheduled new Advisory Committee hearings in December 2010. Virtually all of the Advisory Committee comments were favorable to the IAOMT position. FDA has yet to rule on these Petitions. One of the primary purposes of submitting this position statement is to notify the European Union's Non-food Scientific Committees of FDA's errors in order to eliminate similar mistakes as this issue moves forward.

IV. Risk Assessment Discussion

A. Introduction

Mercury fillings are not safe and should be removed from the market, just as every other mercurial medical device and substance has been. Mercurial wound disinfectants are gone, mercurial diuretics are gone, mercury thermometers are gone, and so are all mercurial veterinary substances. There is no magic that makes dental mercury safer than those obsolete products of the past. In this era when the public is advised to be concerned about mercury exposure through fish consumption, mercury fillings should also be eliminated as the predominant source of mercury exposure in the general population.

An effective and defensible risk assessment complies with the standards of practice endorsed and espoused by the professional risk assessment community. Those standards of practice have been well presented and expressly documented by the U.S. EPA (2004, 1998, 1994) and most recently, by the U.S. National Academy of Sciences (US NAC, 2008). Those standards of practice demand: 1) a methodical analysis of the 'weight of evidence' of the toxicological literature; 2) a detailed quantitative analysis of that toxicological database towards the determination of a defensible regulatory reference exposure level; and 3) a methodical, transparent and defensible quantification of exposure for comparison to that reference exposure level.

B. What is a defensible regulatory risk assessment?

An effective and defensible risk assessment of dental amalgam requires a detailed quantitative analysis of the exposure to mercury vapor in the general population. A typical, defensible regulatory risk assessment for chemical exposure would quantify that exposure in

across the entire general population, and particularly in the 'reasonably maximally exposed' portion of the population, not just some undefined average or typical person. To achieve this, data on the range (minimum to maximum) of that chemical exposure across all members of the general population is required—including those with up to twenty-five amalgam-filled teeth.

Further, a defensible risk assessment does not exclude any segment of the relevant population. This would include children under six years of age, despite it being known that children as young as three years of age do receive amalgam fillings and, as a result, are exposed to mercury vapor from this source. The significance of this is compounded by the fact that risk assessment guidance for neurotoxic agents such as mercury vapor (see USEPA 1998) specifically stipulates the importance of considering infants and young children in whom neurotoxicity will be pronounced due to the susceptibility of the growing and developing brain to the effects of neurotoxins.

To demonstrate that such an exposure assessment is possible and feasible, the Canadian government, in its risk assessment of dental amalgam (Health Canada, 1995)[1] was open and transparent about the prevalence of mercury fillings in the Canadian population, with adults having up to twenty-five filled teeth and children as young as three years of age having filled teeth. Health Canada was also explicit in the methods used to estimate exposures, to the point of providing estimates of mercury vapor exposure per filled tooth, for each of five separate age groups (toddlers, children, teens, adults and seniors). Health Canada neither omitted to determine exposure in persons with more than ten fillings, nor omitted to consider children less than six years of age.

C. What is an appropriate risk characterization? (What reference levels should exposures be compared to?)

The general population should be employed for the assessment of potential risks posed by amalgam. Health Canada (1995), on the other hand, directly compared mercury vapor exposure from dental amalgam to such a reference exposure level specifically derived for the protection of the general population.

D. Doses Associated with the EPA RfC and the ATSDR MRL versus FDA's Ill-Defined Exposure Levels for Adults and Children Six Years of Age and Older

1. Internal doses associated with the RfC and MRL

In its Final Rule, FDA calculated the EPA's Reference Concentration ("RfC) and the Miminum Risk Level ("MRL") established by the U.S. Agency for Toxic Substances and Disease Registry ("ATSDR") to establish an absorbed dose. However, FDA incorrectly estimated the following internal doses:

Age group	RfC-associated intake (µgs /day)	MRL-associated intake (µgs /day)
Adults	4.9	3.2

[1] Richardson, GM, Assessment of Mercury Exposure and Risks from Dental Amalgam (1995).

5 year old Children	2.3	1.5
1 year old Infants	1.7	1.2

In calculating these absorbed doses, the FDA made four key errors:

- it used unreliable values for inhalation rates;
- it failed to adjust the inhaled doses for the 80% absorption of mercury vapor in the lungs, an absorption rate acknowledged elsewhere in FDA's Final Rule;
- it fails to standardize the internal doses associated with the RfC and MRL (and those from amalgam) with various body weights to account for the great weight disparities found in the different age groups under consideration.
- the RfC-associated dose and MRL-associated dose is derived for adults only, the age group studied in the occupational studies upon which the RfC and MRL are based.

2. Proper Inhalation and Absorption Rates

U.S. EPA's Exposure Factors Handbook (EPA 1997) reviews twenty-one key and dependable studies to determine that the adult inhalation rate is 13.25 m3/day for males and females combined. The inhaled absorption rate for mercury vapor is 80%.

3. Standardization to Account for Varying Body Weights

One should convert both the exposure estimate and the reference exposure levels to the same units. To do this, both must be converted to absorbed, weight-standardized doses in units of μgs/kg body weight/day. The internal dose associated with the EPA RfC for mercury vapor (0.3 μgs/m3) can be determined by consideration of inhalation rate and body weight in adults, the population group investigated in the occupational epidemiology study upon which the RfC was based, and adjusting for 80% absorption. According to the U.S. EPA, adult average inhalation rate is 13.25 m3/day (EPA, 1997; average of males and females) and average adult body weight is 71.8 kg (EPA 1997; average of males and females). Assuming that 80% of inhaled mercury vapor is absorbed, the internal RfC-associated reference dose is: (0.3 μgs/m3 x 13.25 m3/day X 80%)/71.8 kg = 0.044 μgs/kg body weight/day. For the MRL of 0.2 μg/m3, the equivalent internal MRL-associated reference dose is similarly derived as 0.03 μg/kg bw/day.

4. Mercury Exposure from Dental Amalgam

The WHO Environmental Health Criteria 118 (WHO 1991) concluded that *"[e]stimated average daily intake and retention"* from dental amalgam was 3.8-21 (3-17) μg/day (values in brackets representing retained (absorbed) dose (WHO, 1991, Table 2). In the Executive Summary of this document (WHO 2003), WHO clearly states *"Dental amalgam constitutes a*

*potentially significant source of exposure to elemental mercury, with estimates of daily intake from amalgam restorations ranging **from 1 to 27 µg/day.**"*

5. Comparing Mercury Exposure from Amalgam to the Reference Exposure Levels for the General Population

In order to compare an assumed mercury vapor dose to the EPA RfC or ATSDR MRL (0.3 µg/m3 and 0.2 µg/m3, respectively), it is necessary to convert both the exposure estimate and the reference exposure level to the same units. To do this, both must be converted to absorbed, weight-standardized doses in units of µgs/kg/bw/day.

If we assume, *arguendo*, that ten amalgam fillings will deliver a daily dose of mercury of five µgs/day as an absorbed dose (FDA's assumption), then one filling delivers an absorbed dose of 0.5 µgs/day. When standardized to body weight, as is routine for toxicological reference exposure levels and exposure assessments, this daily dose represents differing doses for different age groups with differing average body weights. Using data on body weights of different age groups provided by the EPA (2008), the weight-standardized doses associated with that 0.5 µg/day dose are:

Age group	**Body weight**	**Weight-standardized dose per filling (after FDA)**	**Number of fillings to exceed EPA RfC**	**Number of fillings to exceed ATSDR MRL**
3 - 6 year olds	18.6 kg	0.027 µg/kg bw/day	2	2
6 - 11 year olds	31.8 kg	0.016 µg/kg/bw/day	3	2
Teens (12-19 yrs)	56.4 kg	0.009 µg/kg/bw/day	5	4
Adults (≥ 20 yrs)	71.8	0.007 µg/kg/bw/day	7	5

This table clearly demonstrates the following conclusions:

- weight-standardized dose increases as body weight (and age) decreases;
- the weight-standardized dose to young children (aged 3-6 years) is almost four times greater than the weight-standardized dose to adults, due entirely to the difference in body weights between these age groups;
- young children who have two or more amalgam fillings exceed the weight-standardized absorbed dose associated with the EPA RfC and ATSDR MRL;
- Adults with seven or more amalgam-filled teeth will exceed the RfC and with five or more amalgam fillings will exceed the MRL;

- All age groups will exceed the doses associated with U.S. regulatory reference air concentrations with less than the average of seven to ten fillings.

6. NHANES Data

National Institute of Dental and Craniofacial Research (NIDCR) publishes data collected by NHANES on the average number of filled teeth in the American population (*see, e.g.,* http://www.nidcr.nih.gov/DataStatistics/FindDataByTopic/DentalCaries/DentalCariesAdolescents12to19). NIDCR possesses the data to permit an accurate accounting of the number of persons with filled teeth in the U.S. population. These data would permit an accurate determination of mercury exposure across the full range of numbers of filled teeth in the U.S. population. Richardson has already used these data to demonstrate the "large" percentage of U.S. citizens with amalgam fillings who absorb mercury in excess the EPA RfC and the ATSDR MRL.[2]

Similarly, Al-Saleh, *et al.*[3], found that children with amalgam fillings had significantly more mercury in their urine and hair. Ominously, significant numbers of children with and without amalgam fillings had mercury levels exceeding the acceptable reference limits, leading the authors to conclude that their findings were "alarming."

7. The EPA RfC and the ATSDR MRL are Outdated[4]

Richardson correctly argues that the RELs established by the EPA, ATSDR, and California EPA are no longer valid. (Richardson, *et al.* (2011), Section 4.3) The most recent review of the toxicological literature relating to mercury vapor by a national or international environmental health agency was prepared by Health Canada (2006), which was subsequently published in the scientific literature by Richardson, *et al.* (2009).[5] Richardson established an REL for public health protection and risk assessment of 0.06 μgs/m³. This REL is now employed by Health Canada for environmental risk assessment of Hg^0 exposures. Lettmeier *et al.* (2010) recently proposed a REL of 0.07 μg Hg^0/m^3 based on an airborne Hg^0 LOAEL

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[2] Richardson, GM, *et al., Mercury Exposure and Risks from Dental Amalgam in the US Population, post-2000*, Science of the Total Environment, 409 (2011) 4257–4268 (Table 6).

[3] Al-Saleh, *et al., Mercury (Hg) burden in children: The impact of dental amalgam*, Science of the Total Environment 409 (2011) 3003-3015.

[4] In this section of the paper (section 9), there are several incomplete references to published papers identified only by author and year. Each of these papers is discussed in Richardson, G.M., *et al., Mercury vapour (Hg^0): Continuing toxicological uncertainties, and establishing a Canadian reference exposure level.* Regulatory Toxicology and Pharmacology, 53: 32-38 (2009). The complete citations can be obtained from this article.

[5] Richardson, G.M., *et al., Mercury vapour (Hg^0): Continuing toxicological uncertainties, and establishing a Canadian reference exposure level.* Regulatory Toxicology and Pharmacology, 53: 32-38 (2009).

concentration of 3.5 μgs Hg°/m^3 (equivalent to their LOAEL urine Hg concentration). Health Canada's up-to-date REL (analogous to EPA's RfC) for mercury vapor is some five times lower than the out-of-date EPA RfC of 0.3 ug/m^3, and more than three times lower than the ATDSR's out-of-date MRL.

Most of the occupational studies underlying our knowledge of mercury vapor toxicity and, therefore, underlying all current RELs for Hg°, were conducted on chloralkali workers. Although air–Hg° concentrations are generally elevated among such workers, concomitant exposure to chlorine gas (Cl2) occurs. Data on airborne Cl2 levels in chloralkali plants were recently summarized by the European Union (EU, 2007). Cl2 levels in the air of chloralkali plants averages about 1 ppm (0.3 mg/m3) and ranges between 0 ppm and 6.5 ppm (0–19.5 mg/m3) depending on the specific work environment where sampling was conducted.

The concomitant exposure to Cl2 and Hg° effectively reduces worker exposure by decreasing the amount of airborne Hg° available for inhalation and absorption. Mercury converts to HgCl2 in the presence of Cl2 at room temperature (Menke and Wallis, 1980; Viola and Cassano, 1968). The inhalation absorption of HgCl2 is only half or less of that of Hg° (ATSDR, 1999; Viola and Cassano, 1968). Hg° deposition to the brain is also altered. Hg^{2+} (associated with HgCl2) does not cross the blood–brain barrier as does Hg° (Lorscheider *et al.*, 1995; Viola and Cassano, 1968). Following Hg° exposure, the red blood cell (RBC) to plasma Hg° concentration ratio typically ranges between 1:1 and 2:1 (WHO, 1991). However, much less Hg° is associated with RBCs in the blood of chloralkali workers (with Cl2 present).

Suzuki, *et al.* (1976), investigating Hg°-exposed chloralkali workers versus workers from two other industrial sectors (who were all exposed to Hg° at similar airborne concentrations (0.01–0.03 mg/m3)), observed that the RBC to plasma Hg° concentration ratio in the chloralkali workers was only 0.02:1 whereas workers of the two other industries (with no concomitant exposure to Cl2), had RBC to plasma Hg concentration ratios between 1.5:1 and 2:1. A study by Viola and Cassano (1968) of rodents (rats, mice) exposed to Hg° alone or in the presence of Cl2, demonstrated reduced Hg° absorption in the presence of Cl2 and the deposition of Hg° to the brain of rodents exposed concomitantly to Hg° and Cl2 was only 1/5th of that when exposure was to Hg° alone.

There is other evidence of the interaction of Cl2 with Hg°. Cl2 injection is employed as a direct Hg° emissions control technology to reduce Hg° levels in industrial stack emissions (Pavlish *et al.*, 2003). Increasing chlorine quantity/concentration in the process improves the efficiency of Hg° emission control (Richards, 2005). In the presence of chlorine, Hg° is converted to Hg^{2+}, which precipitates with stack particulate matter that is subsequently removed ('scrubbed') from stack emissions.

It is evident, therefore, that all studies of uptake and toxicity of Hg° exposure in chloralkali workers will be confounded by concomitant Cl2 exposure and, as a result, studies of chloralkali workers should not form the primary basis for a REL for Hg°; the application and extrapolation of those results to other occupational groups and the general public, whose Hg° exposure occurs in the absence of Cl2, is invalid.

8. Current EPA Guidelines Require Updated Uncertainty Factors

The guidelines on risk assessment of neurotoxic agents (EPA 1998) clearly indicate that an uncertainty factor of ten should be applied when attempting to extrapolate a lowest-observed-adverse-effect-level (LOAEL) to establish an REL, as is the case for studies of mercury vapor toxicity – the threshold cannot be determined from available studies. The guidelines on risk assessment of neurotoxic agents also clearly indicate that an uncertainty factor of ten should be applied to address inter-individual variability in susceptibility to the toxic effects of neurotoxins such as mercury vapor. This would create a total uncertainty factor adjustment of 100. The EPA RfC for mercury vapor, which predates EPA's 1998 guidance on the risk assessment of neurotoxins, only applied a total uncertainty adjustment of thirty, an adjustment now out of compliance with EPA policies.

Further modifying factors may also be considered by the EPA when they re-assess mercury vapor neurotoxicity, that modifying factor addressing other deficiencies and limitations in the toxicological database on mercury vapor. Those deficiencies and limitations may include, but not be limited to, the following:

a. Gender Differences in Hg Pharmacokinetics

Recent evidence indicates clear gender differences in uptake, distribution, and excretion of Hg°. Studies indicate that males metabolize and eliminate Hg° more quickly than do females and that, after exposure, Hg° tends to be distributed differently in males and females, with a greater proportion of dose going to the brain and CNS of females. While Hg° appears to be distributed more quickly to the kidney and urine in males, it appears to be retained for a longer time in females and thus be potentially more available to illicit toxic response in females.

b. Genetic predisposition to Hg toxicity

Echeverria, *et al.*[6], identified polymorphisms in genes encoding for brain-derived neurotrophic factor (BDNF). Various detriments in neurobehavioral performance were associated with the presence of the BDNF polymorphism (frequency = _25–35% among study subjects (193 male dentists; 233 female dental assistants)), independent of Hg exposure level. The combined effects of the polymorphism and Hg exposure appeared to be additive. These results suggest that the presence of the polymorphism does not necessarily put persons at risk of an enhanced toxic response to Hg exposure. Rather, persons with the polymorphisms might respond to Hg exposures similarly to those without, but from a diminished starting point with respect to neurobehavioral performance.

The presence of a polymorphism for coproporphyrinogen oxidase (CPOX4; frequency = 15% of subjects in Woods, *et al.* (2005); and 25% of study subjects in Echeverria, *et al.* (2006))

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[6] Echeverria, D., *et al.*, *The association between a genetic polymorphism of coproporphyrinogen oxidase, dental mercury exposure and neurobehavioral response in humans*, Neurotoxicology and Teratology, 28 (2006) 39-48.

has also been observed and is associated with detriments in neurobehavioral response independent of Hg exposure. As with BDNF, the influence of the CPOX4 polymorphism and Hg exposure appeared to be additive.

In the Casa Pia children's amalgam trial, DeRouen, *et al.*[7], found no association between Hg body burden and the production of porphyria. In contrast, in reviewing the same data set, Geier, *et al.*[8], found the characteristic pattern of porphyria associated with Hg body-burden, which were significantly correlated with dental amalgam exposure in a dose-dependent fashion.

V. Occupational Exposure to Mercury and Injuries Caused Thereby

Dentists and their staff are exposed to mercury at a greater rate than their patients. Catastrophic exposures from past practices include hand-squeezing of fresh amalgam, where drops of liquid mercury would run over the dentist's hands and contaminate the entire office. Recent research has demonstrated that dangerous levels of mercury and amalgam particulate are generated in the dental workplace. Eighty-five percent of dentists have aberrant porphyrin metabolism, characteristic of low level mercury poisoning.[9]

Chronic exposure to mercury for dental patients does not exist where alternative materials are used for new fillings. However, there is a high risk of exposure when old fillings are drilled out, and the challenge for the future will be to train dentists to be cautious as they remove the thousands of tons of mercury currently stored in the amalgam fillings of the American population. Using standard exposure assessment methods,[10] Dr. G. Mark Richardson, the author of the 1996 Health Canada risk assessment study on dental amalgam,[11] estimated that a dentist who removes four amalgams per day will inhale 38 milligrams of mercury derived from amalgam particulate. Dr. Richardson was an expert witness for Dr. David Barnes in litigation against amalgam manufacture Kerr Corp. (discussed below.) In assessing Dr. Barnes's

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[7] DeRouen TA, (2002) Control Clin Trials 23(3):301–320.

[8] Geier, DA, *et al., 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) 24:215-224.

[9] Echeverria D., *et al.*, "*Chronic low-level mercury exposure, BDNF polymorphism, and associations with cognitive and motor function.*" Echeverria D, Woods JS, Heyer NJ, Rohlman DS, Farin FM, Bittner AC Jr, Li T, Garabedian C (2005).

[10] Richardson, G.M., *Inhalation of Mercury-Contaminated Particulate Matter by Dentists: An Overlooked Occupational Risk*, Human and Ecological Risk Assessment, 9:1519-1531 (2003).

[11] Health Canada. "*Assessment of Mercury Exposure and Risks From Dental Amalgam: Final Report.*" Richardson, G.M., Ph.D., Medical Devices Bureau, Environmental Health Directorate.

occupational exposure to mercury, Dr. Richardson estimated that Dr. Barnes was absorbing between 8019 and 8779 micrograms ("µgs") of mercury into his blood stream every workday.

A number of studies demonstrating neurobehavioral deficits in dental personnel have been published.[12] [13] [14] [15] [16] [17] Dentists with occupational exposure to mercury score below normal on neurobehavioral tests of motor speed, visual scanning, verbal and visual memory, and visuomotor coordination.[18]

Studies demonstrate the neurobehavioral effects of elemental mercury on dentists.[19] One study detected "significant [central nervous system] effects" among dentists and dental assistants at very low levels of Hg^0 exposure (i.e. urinary Hg^0 ‹ 4 µgs/liter). Significantly, the authors concluded that "[t]he pattern of results, comparable to findings previously reported among subjects with urinary Hg^0 › 50 µgs/liter, presents convincing new evidence of adverse CNS effects associated with low Hg^0 exposures within the range of that received by the general population." This finding demonstrates adverse neurobehavioral deficits in dentists and dental assistants at urine mercury levels essentially equivalent to the urine mercury levels of those people in whom amalgam has been placed.

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[12] Ngim, C.H., *et al.*, *Chronic Neurobehavioral Effects of Elemental Mercury in Dentists*, Brit J Indust Med, 49:782-90, 1992.

[13] Gonzalez-Ramirez, D., *et al.*, *Sodium 2,3-Dimercaptopropane-1-Sulfonate Challenge Test for Mercury in Humans: II. Urinary Mercury, Porphyrins and Neurobehavioral Changes of Dental Workers in Monterrey, Mexico.*

[14] Shapiro, I.M., *et al.*, *Neurophysiological and neuropsychological function in mercury-exposed dentists.* Neurotoxicol Teratol, 17(2):161-8 (1995).

[15] Standard medical textbooks also recognize this phenomenon. *See* Harrison's Principles of Internal Medicine, 14th Edition.

[16] Echeverria, D., *et al.*, *Behavioral Effects of Low-Level Exposure to Hg^0 Among Dentists.* J Pharmocol Exper Therap, 272(1):264-74 (1995).

[17] The Lancet 1, 1147-1150 (1982); Uzzell, B.P., *et al.*, *Chronic low-level mercury exposure and neuropsychological functioning.* J of Clin and Exper Neuropsych. 8, 581-593.

[18] Harrison's Principles of Internal Medicine, 14th Edition at 2567.

[19] Echeverria, *et al.*, *Neurobehavioral Effects from Exposure to Dental Amalgam Hg^0: New Distinctions Between Recent Exposure and Hg Body Burden,* FASEB J. 12, 971-980 (1998).

In Germany in 1994, the Department of Health conducted a peer-reviewed scientific assessment of the safety of dental amalgam. Arguments for amalgam safety were based upon occupational workplace standards. The reviewers concluded that arguments for safety failed to establish their point for two reasons. Some individuals who are outliers in exposure exceeded these standards. Furthermore, occupational standards are for a 40-hour week and when converted to a 24/7 (168-hour) basis an even greater percentage of the population is exposed to mercury at and above this standard, which clearly was never intended to protect vulnerable subsets of the population.[20]

The current scientific data indicates that female dental personnel are severely impacted by occupational exposure to mercury. The Occupational Safety and Health Act (OSHA) has recommended no exposure of fertile women to amounts of mercury greater than 10 micrograms per cubic meter of air, and pregnant women should be occupationally exposed to no mercury. These recommendations are not being followed by the dental industry, and there is substantial scientific evidence that even these modest measures would not fully protect dental workers. Research has shown that mercury even in extremely small amounts has toxic effects on the neurological system, including cytotoxicity to nerve tissue.[21] [22] [23] [24] [25] [26] [27] [28] [29] [30] [31] [32]

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[20] Friberg, L.T., *et al., Status Quo and Perspectives of Amalgam and other Dental Materials*, International Symposium Proceedings Georg Thieme Verlag Stuttgart - ISBN 3-13-102471-2 New York 1995.

[21] Sharma, R.P., *et al.*, "*Metals and Neurotoxic Effects: Cytotoxicity of Selected Metallic Compounds on Chick Ganglia Cultures.*" Journal of Comp. Pathology Vol. 91, 1981.

[22] Leirskar, J., "*On the mechanism of cytotoxicity of silver and copper amalgams in a cell culture system.*" Scand J Dent Res 82:74-81, 1974.

[23] Wedeen, R.P., "*Lead, Mercury and cadmium nephropathy.*" Neurotoxicology (Park Forrest Ill, 4(3): 134-146, 1983.

[24] Weening, J.J., *et al.*, "*Autoimmune reactions and glomerulonephritis caused by heavy metals and other toxins.*" Dev Toxicol Environ Sci, 11: 211-216, 1983.

[25] Weening, J.J. *et al.*, "*Mercury induced immune complex glomerulopathy: an experimental study.*" Chapter 4: pp 36-66. VanDendergen, 1980.

[26] Koller, L.D., "*Immunotoxicology of heavy metals.*" Int J Immunopharmacol , 2:269-279, 1980.

Dentists' exposure to mercury is associated with many health problems, most notably birth defects and neurological disorders.[33] [34] [35] [36] [37] A 1987 study by Sikorski identified a significant positive correlation between mercury levels in the hair of occupationally exposed

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[27] Koller, L.D., "*Immunosuppression produced by lead, cadmium, mercury.*" Am J Vet Res. 34:1457-1458, 1973.

[28] Koller, L.D. *et al.*, "*Immuno response in rats supplemented with selenium.*" Clin Exp Immunol. 63 (3) :570-576, 1986.

[29] Fiskesjo, G., "*The effect of two organic mercury compounds on human leukocytes in vitro.*" Hereditas. 64:142-146, 1970.

[30] Gerstner, H.B., *et al.*, "*Clinical Toxicology of Mercury.*" Journal of Toxicology and Environmental Health. Vol 2, Issue 3 (491-526), 1977.

[31] Verschaeve, L. *et al.*, "*Genetic Damage induced by Occupational Low Mercury Exposure.*" Environmental Research. Vol 12, (306-316) (1976.).

[32] Nordberg, G.F., ed., "*Effects and Dose Response Relationships of the Toxic Metals.*" New York: Scientific Publishing Co 1976.

[33] Gordon H., "*Pregnancy in female dentists - A mercury hazard.*" In proceedings of the International Conference on Mercury Hazards in Dental Practice Gloscow, Scotland 2-4 Sept 1981.

[34] Panova, Z., *et al.*, "Ovarian function in women having professional contact with mercury." Akusherstvoi Ginekologiya 13(1) : n29-34, 1974.

[35] Noe, F.E., "*Mercury as a potential hazard in medical laboratories.*" New Eng J Med 261:1002-6, 1959.

[36] Cook, T., *et al.*, "*Fatal mercury intoxication in a dental surgery assistant.*" British Dent J. 127(12):553-555, Dec 1969.

[37] Marinova, G., *et al.*, "*A study of the reproductive function in women working with mercury.*" Problemi na akuserstvoto i Ginekologiyata 1:75-77, 1973.

women and the occurrence of reproductive failures and menstrual cycle disorders.[38] One published account reports that a young dentist, professionally exposed to mercury for 35 weeks during her pregnancy, delivered a severely brain-damaged mercury-poisoned infant.[39]

The textbook, *Occupational Hazards in the Health Professions*, cautions against comprehensive amalgam work during pregnancy.[40] Koos and Lango stated that fertile women should be exposed to mercury concentrations not exceeding 10 µg/m3, and pregnant women should be exposed to no mercury at all.[41] Such exposures cannot be avoided by women who work in the field of dentistry.[42]

Clearly, women in dentistry are not only at the greatest risk from exposure to mercury, but they are not being adequately protected. The United States Environmental Protection Agency states that, "Women chronically exposed to mercury vapor experience increased frequency of menstrual disturbances and spontaneous abortions; also a high mortality rate was observed among infants born to women who displayed symptoms of mercury poisoning."[43]

Indeed, an assistant's death was reported in 1969 from kidney failure.[44] The kidney filters the blood and, as a result, chronic exposure to chemicals can eventually induce kidney damage. A 1988 study by Verschoor, *et al.* evaluated the kidney function of 68 dentists (63 men, 5 women) and 64 female assistants who were apparently healthy, not pregnant, and taking no drugs. They

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[38] Sikorski, R., *et al.*, "*Women in dental surgeries: reproductive hazards in occupational exposure to metallic mercury.*" Int Arch Occup Environ Health. 59 (6):551-557 (1987.)

[39] Gelbier, S., *et al.*, "*Possible fetotoxic effects of mercury vapor: a case report.*" Public Health 103(1):35-40 1/1989.

[40] Brune, D.K., *et al.*, "*Occupational Hazards in the Health Professions*," Chapter 16, 315-316 Boca Raton Fl: CRC Press, Inc. (1989).

[41] Koos, B.J., *et al.*, "*Mercury Toxicity in the pregnant woman, fetus, and newborn infant.*" A review Am J Obstetrics and Gynocology 126(3):390-409 (1976).

[42] Eggleston, D.W., "*Dental Amalgam -- To Be or Not To Be*," Pacific Coast Society of Prosthodontists Newsletter 9(2):4-10 10,1989.

[43] U.S.E.P.A. Mercury Health Effects Update. Final Report (1984)EPA-600/8-84-019F United States Environmental Protection Agency, Office of Health and Environment Assessment. Washington, D.C. 20460.

[44] Cook, T., *et al.*, "*Fatal mercury intoxication in a dental surgery assistant.*" British Dent J. 127(12):553-555, Dec 1969.

compared the results of their kidney function analysis to 250 workers known to be exposed through the workplace to lead, cadmium, or chromium. Their conclusion was that, "Dentists and dental assistants appear to have a higher potential risk of kidney function disturbances than the workers in these industries. Although this study did not present evidence for changes of renal function parameters in dental practice in relation to Hg-urine levels below 20 µg/l, it certainly suggests that dental practice may carry a risk of renal dysfunction. There is a need to assess the renal hazard of the potential nephrotoxic chemicals used in dental practice."[45] This study also demonstrates the need to assess the adverse effects of mercury fillings on kidneys against a control cohort of healthy subjects, not workers exposed to other confounding toxins.

Furthermore, Kuntz followed 57 prenatal patients with no known exposure to mercury for changes in whole blood from initial prenatal examination to delivery and postpartum hospitalization. The mothers' whole blood total mercury increased during pregnancy from .79 ppb at initial examination to 1.16 ppb at delivery. This represents a 46% increase during pregnancy. Mercury has previously been recognized for its particular ease of crossing the placental membrane. The umbilical cord blood was also sampled at birth and found to have even higher levels of mercury at 1.5 ppb.[46] After careful analysis of the data, Kuntz concluded: "Previous stillbirths, as well as history of birth defects, exhibited significant positive correlation with background mercury levels." He further stated that patients with large numbers of dental fillings exhibited a tendency to higher maternal blood levels, which agrees with both Ott and Abraham. [47]

Vimy confirmed the transport of mercury from fillings to the fetus in experimental animals (sheep and monkey), and the additional exposure through mothers' milk.[48] Berlin has shown the fetal blood content of mercury was raised dramatically at the end of pregnancy exceeding that of the mother at delivery by a factor of at least five. Early abortion, premature birth, and low birth weight with a perinatal death, have been observed in monkeys.[49]

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[45] Verschoor, M.A., *et al.*, "*Urinary Mercury Levels and Early Changes in Kidney Function in Dentists and Dental Assistants.*" Community Dentistry and Oral Epidemiology, Vol. 16 #3.

[46] Pitkin, R.M., *et al.*, *Mercury in human maternal and cord blood, placenta and milk.* Soc Exper Biol Med Proc 1976: 151: 565-7.

[47] Kuntz, W.D., *et al., Maternal and Cord Blood Background Mercury Levels: a longitudinal surveillance.* Am J Obstet Gynecol 143(4):440-3, 1982.

[48] Vimy, M.J., *et al., Maternal-Fetal Distribution of Mercury (203 Hg) Released from Dental Amalgam Fillings.* Journal of American Physiological Society, April 1990.

[49] Berlin, M., *et al.,* University of Lund, Institute of Environmental Medicine, Lund Sweden (Abstract The Toxicologist 31st Annual Meeting Vol 12 #1 February 1992).

Mikhailova, *et al.* found that 26.8% of women working in a mercury polluted atmosphere suffered from menstrual disturbances. Marinova, *et al.* found that 29% had hypermenorrhea.[50] The controls found only 0.3% with the same condition. Hypomenorrhea occurred in 15.3% of the exposed group and only 0.6% of the nonexposed group. This could mean that more than 44% of female dental personnel working under these conditions will suffer from reproductive disorders due to mercury in the dental office. This hypothesis is corroborated by two other studies of women occupationally exposed to mercury, which found that 36% to 45% will develop these types of disorders within 6 months of employment, a proportion that increases to 67% within three years of employment.[51] [52]

This hypothesis has been further confirmed in a recent study of 418 women working in dentistry who became pregnant during the previous four years. Detailed information was collected on mercury-handling practices and the number of non-contracepting menstrual cycles it took the women to become pregnant. Dental assistants not working with amalgam served as unexposed controls. Women working in offices with poor mercury hygiene factors took longer to become pregnant. The fecundability (probability of conceiving in any given menstrual cycle) of this high exposure group was only 50% of that for unexposed women after controlling for age, smoking, race, frequency of intercourse, history of pelvic inflammatory disease, year the attempt began, and occupational exposure to cold sterilants, x-rays, and unscavenged nitrous oxide.[53]

The most common symptoms were dysmenorrhea (painful menstruation), hypermenorrhea, anovulation (infertility >40%), and hypomenorrhea. These symptoms are

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[50] Mikhailova, L.M., *et al.*, *The influence of occupational factors on disease of the female reproductive organs*. Pediatriya Akusherstvoi Ginekologiya. 33(6)56-58, 1971.

[51] Panova, Z., *et al., Ovarian function in women having professional contact with metallic mercury.* Akusherstvoi Ginekologiya 13(1):29-34, 1974.

[52] Goering, P., *et al.*, *Toxicity Assessment of Mercury Vapor from Dental Amalgams*, Fundamental and Applied Toxicology, 19, 319-329 (1992).

[53] Rowland, A., *et al., A Reduced Fertility Among Dental Assistants With Occupational Exposure to Mercury,* National Institute of Environmental Health Sciences, Research Triangle, NC (Abstract The Toxicologist 31st Annual Meeting Vol 12 #1 February 1992).

known to increase in populations additionally exposed to lead.[54] The relationship between spontaneous abortion, stillborn infants, and mercury has also been confirmed.[55]

Problems that may develop in the fetus from maternal exposure are not always evident at birth. Prenatal exposure to mercury vapor has been shown to have an effect on brain development. Such delayed problems include diminished learning capacity, muscle spasms, and altered electroencephalograms.[56] Exposure continues to increase if the infant is nursed, since mercury concentrates eight-fold in breast milk.[57] [58]

In a study of the relation between cumulative exposure to mercury and chronic health impairment, conducted by Dr. Shapiro and associates in 1982, 298 dentists had their mercury levels measured by an X-ray fluorescence technique.[59] Electrodiagnostic and neuropsychological findings in the dentists with more than 20 micrograms/g tissue mercury levels were compared with those of a control group consisting of dentists with no detectable mercury levels. Thirty percent (30%) of the 23 high mercury dentists had polyneuropathies. No polyneuropathies were detected in the control group. The high mercury group had mild visuographic dysfunction; they also had more symptom-distress than did the control group. These findings suggest that the use of mercury as a restorative material is in fact a health risk for dentists.

In a series of experiments utilizing neutron activation analysis (NAA) to study the mercury content of brain tissues of amalgam bearers, non-amalgam bearers, and dentists, Dr. Magnus Nylander found in the cases of seven dentists and one dental nurse that all had a surprisingly high pituitary mercury content, totally out of proportion to the content found in other

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[54] Yang, S., *Influence of lead on female reproductive function.* Chung Hua Fu Chan Ko Tsa Chih, 21(4):208-210, Jun 1986 (English abstract p 252).

[55] Koos, B.J., *et al., Mercury Toxicity in the pregnant woman, fetus, and newborn infant.* A review Am J Obstetrics and Gynecology 126(3):390-409, 1976.

[56] Dencker, *et al.*,University of Uppsala (Abstract The Toxicologist 31st Annual Meeting Vol 12 #1 February 1992).

[57] Pierce, P., *et al., Alkyl mercury poisoning in humans. Report of an outbreak.* JAMA 220:1439-1442, 1972.

[58] Snyder, R.D., *Congenital mercury poisoning.* N Eng J Med. 18:1014-1016, 1971.

[114] Shapiro, I.M., *et al., Neurophysiological and neuropsychological function in mercury-exposed dentists.* Lancet 1982;22:1147-1150.

parts of the brain. Values ranged from 135 to 4,000 nanograms Hg per gram tissue.[60] [61] He also found in a related study of dentists and dental assistants in Sweden that they have twice the incidence of brain tumors as non-dental personnel.[62]

Most recently, Duplinsky, *et al.*[63], determined that dentists are not as healthy as matched controls from the general population. Using pharmacy utilization data to evaluate the health status of 600 dentists, dentists demonstrated significantly more prescription utilization of specific illness medications than the controls. The diminished health status of the dentists was attributed to their occupational exposure to mercury.

VI. Mercury Has Been Identified in a Large Number of Peer-Reviewed Studies As Being a Likely Cause of the More Prevalent Neurological Disorders Such as Alzheimer's Disease, Severe Autism, Multiple Sclerosis, ALS, and Parkinson's Disease. It also causes Kidney Disfunction, Hearing Loss, Allergy, and Periodontal Disease.

As a preliminary matter, we notice that FDA declined to consider review articles on the ostensible basis that they present no new empirical data for consideration. FDA then relies on assurances of amalgam safety announced in a 2004 review article prepared by LSRO as the ostensible basis for generally refusing to consider articles published prior to LSRO's review. It seems as a matter of simple objectivity that review articles are either to be considered or they are not. If FDA is willing to consider LSRO's review article, it should consider the dissenting opinions set forth in some of the review articles identified herein. It appears to us that an objective FDA would heed the rejection of the FDA's White Paper by FDA's own hand-picked Joint Panels in 2006 and question the proclamations of safety previously announced by LSRO in 2004. Instead, FDA rejects the announcements of its advisory panels and accepts without question the questionable views of LSRO. Following is a more robust discussion of the literature associating various diseases and conditions with exposure to mercury.

A. Alzheimer's Disease

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[60] Nylander, M., *Mercury in pituitary glands of dentists*. Lancet 442, Feb 22, 1986.

[61] Friberg, L., *et al.*, *Kvicksilver i centrala nervsystemet i relation till amalgamfyllningar (Mercury in the central nervous system in relation to dental amalgam).* Lakartidningen 83:519-22, 1986.

[62] Ahlbom, A., Norell, S., Rodvall, Y., and Nylander, M., *Dentists, dental nurses, and brain tumors.* Br. Med. J., 292, 662, 1986.

[63] Duplinsky, *et al.*, *The Health Status of Dentists Exposed to Mercury from Silver Amalgam Tooth Restorations*, International Journal of Statistics in Medical Research, 2012, 1, 1-15.

There are a number of very serious neurological disorders for which the cause is mysterious. The clinical pictures of several of these are most interesting when considered in light of the documented neurotoxicity of mercury and the potential for neurotoxicity from mercury/silver fillings.

Despite the protests of the FDA and the ADA, the science confirms that these fillings emit significant levels of neurotoxic mercury, and mercury is injurious to human health. This mercury from fillings would certainly exacerbate and probably is the cause of Alzheimer=s, Multiple Sclerosis, Parkinson's, autism and ALS (Lou Gehrig=s Disease). The synergistic effects of mercury[64] with many of the toxicants commonly found in our environment make the danger of mercury unpredictable and possibly quite severe, especially any mixture containing elemental mercury, organic mercury, and other heavy metal such as lead and aluminum.

Mercury has been linked to Alzheimer=s disease by a number of different studies that have accumulated over the last two decades. In 1986, Ehmann reported that samples of AD brain analyzed by neutron activation had significantly elevated amounts of Hg in every area analyzed. In some areas such as the cerebellar hemisphere Hg levels were ten-fold greater in AD than controls (table 4).[65] The elevated Hg imbalance in AD brain was confirmed in a follow up studies by Thompson and others (1998).[66] Through cell fractionation, Wenstrup was able to trace the accumulation of mercury into the cell organelle called the mitochondria (1990).[67] Mitochondria are tiny organelles contained within cells that produce protein. These papers were all published in high quality scientific journals that were expert in reviewing such analytical data.

Later a paper was published in the Journal of the American Dental Association (JADA) that supposedly refuted these findings (Saxe 1995).[68] It should be noted that this publication in the JADA is in a journal with no expertise in reviewing the analytical chemistry or the neurology involved and has been highly criticized for its unwarranted conclusions. However, even in this paper, the mercury levels in the brains of Catholic nuns showed many of the Sisters had levels of

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[64] Schubert, *et al.*, "*Combined Effects in Toxicology—A Rapid Systematic Testing Procedure: Cadmium, Mercury & Lead.*" J. of Toxicology & Environmental Health, 4:763 (1978).

[65] Ehmann, W.D. *et al.*, *Application of Neutron Activation analysis to the Study of Age Related Neurological Diseases*, Biol Trace Elem Res. 13:19-33 (1987).

[66] Thompson, *et al.*, *Regional Brain Trace-element Studies in Alzheimer=s Disease*, Neurotoxicology, 9(1):107 (Spring 1988); Vance, *Trace Element Imbalances in Hair and Nails of Alzheimer=s Disease Patients*, Neurotoxicology, 9(2):197-208 (Summer 1988); Cornett, *et al.*, *Imbalances of Trace Elements Related to Oxidative Damage in Alzheimer=s Disease Brain*, Neurotoxicology, 19(3):339-45 (June 1998).

[67] Wenstrup, *et al.*, *Trace Element Imbalances in Isolated Subcellular Fractions of Alzheimer=s Disease Brains*, Brain Res, 12;533(1): 125-31 (Nov. 1990).

[68] Saxe SR, *et al.*, *Dental amalgam and cognitive function in older women: findings from the nun study*. J Am Dent Assoc. 1995; 126:1495–1501.

mercury that would have to be considered toxic by any scientific standard. Why some nuns living in the same quarters and eating the same food had such elevated levels of mercury shows that it is most likely the ability, or inability, to excrete mercury places an individual at danger for retaining high mercury levels in the brain. Mercury(II) or Hg2+, is neurotoxic and is known to be the most potent causation of oxidative stress, a biochemical state that is widely known to exist in Alzheimer's disease and other neurological illnesses. The *Saxe* study is dealt with in more depth below.

When exposed to normal brain tissue homogenates or neurons in culture Hg2+ (a/k/a, mercury(II) or mercuric mercury) is capable of producing many of the same biochemical aberrancies found in Alzheimer's diseased (AD) brain. Rats exposed to Hg° vapor show some of these same abnormalities in their brain tissue. Specifically, the rapid inactivation of the brain thiol-sensitive enzymes (tubulin, creatine kinase and glutamine synthetase) occurs after: (a) the addition of low micromolar levels of Hg2+, (b) exposure to Hg° or, (c) the addition of Thimerosal (ethylmercurythiosalicylate sodium salt). Moreover, these same enzymes are significantly inhibited in the AD brain. Exposure of neurons in culture to nanomolar levels of Hg2+ has been shown to produce three of the widely accepted pathological diagnostic hallmarks of AD. These AD hallmarks are elevated amyloid protein, hyper-phosphorylation of Tau, and formation of neurofibrillary tangles (NFTs).[69]

In 2001, the University of Calgary researchers, Leong, *et al.* produced a short video visually showing the disruption of tubulin-neurofibril interaction that represents how mercury, and only mercury, can cause synaptic neurodegeneration by destroying neuron growth cones. The cultured neurons exposed to low levels of mercury degenerated in a manner indicative of lesions observed in Alzheimer=s brain. This can be viewed on YouTube.[70] It is important to note that the level of mercury added to the cell culture in this video was one hundred times lower than is typically detected in the cerebral spinal fluid of those with mercury/silver amalgam tooth fillings. The Leong paper is important as it demonstrates that mercury, and only mercury, produces neurofibillary tangles (NFTs) the major diagnostic hallmark of AD. [71] This paper was omitted from FDA's consideration because it is an *in vitro* study, but it is an important paper because it confirms the hypotheses of other papers. Leong supports the earlier reported Hg^{2+} specific destruction of the viability of brain tubulin.[72] Professor Boyd Haley concluded in 2003 that Amercury and other blood-brain permeable toxicants that have enhanced specificity for

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[69] Haley, B.E., *The relationship of the toxic effects of mercury to exacerbation of the medical condition classified as Alzheimer=s disease,* Medical Veritas 4 (2007) 1510B1524.

[70] How Mercury Causes Brain Neuron Degeneration (video)
http://www.youtube.com/watch?v=VImCpWzXJ_w

[71] Leong C.C.W., Syed N.I., Lorscheider F.L., *Retrograde Degeneration of Neurite Membrane Structural Integrity of Nerve Growth Cones Following in vitro Exposure to Mercury* NeuroReport Vol. 12 #4, 2001.

thiol-sensitive enzymes are the etiological source of AD. Included in this category are other heavy metals such as lead and cadmium that act synergistically to enhance to toxicity of mercury and organic-mercury compounds.@[73] The demonstrated toxic synergy of mercury with other heavy metals is a concept completely omitted from consideration in FDA's Final Rule.

Haley found that mercury is the only heavy metal and apparently the only toxin of any kind that can cause many the biochemical abnormalities found in AD brain. The demonstrated synergistic potentiating of mercury toxicity by other heavy metals (lead, cadmium, silver, etc.) explains why a direct correlation between mercury levels alone and severity of AD-like brain damage has not been demonstrated.

Studies done on about five hundred sets of identical twins from WW II veterans show that AD is definitely not a directly inherited disease, as it requires a toxic insult.[74] Certainly, all the information and scientific studies point to toxin(s) as the major cause of AD. Ely confirmed substantial release of mercury from in situ amalgams and estimated the AD population would grow from its 2001 level of four million to fourteen million based upon population age alone.[75] This enormous increase will devastate any health care system as cost of providing for even the 4 million AD patients at present dwarfs the total cost of dental care.

Haley, *et al.*, detailed why the apolipoprotein-4 genotype represents a genetic susceptibility to mercury toxicity as a pathogenetic factor and a moderator of AD.[76] Mutter also demonstrates that persons of African descent have a much higher level of the susceptible APO-E4 gene. This may explain why AD is more prevalent in those with an African heritage.

In 1997, APO-E4 was identified as a significant risk factor for early onset of Alzheimer's with APO-E2 being identified as protective against AD.[77] Several subsequent papers failed to

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[72] Pendergrass, J. C. *et al*, *Mercury Vapor Inhalation Inhibits Binding of GTP to Tubulin in Rat Brain: Similarity to a Molecular Lesion in Alzheimer=s Disease Brain.* Neurotoxicology 18(2), 315-324 (1997).

[73] Haley, B., *The Relationship of the Toxic Effects of Mercury to Exacerbation of the Medical Condition Classified as Alzheimer=s Disease*, The Nordic Journal of Biological Medicine (June-July 2003).

[74] Breitner, J.C.S., *et al.*, *Alzheimer's disease in aging twin veterans. III.* Archives of Neurology, 52:763-771 (1995).

[75] Ely, J.T.A., *Mercury Induced Alzheimer=s Disease: Accelerating Incidence?*, Bull Environ Contam Toxicol (2001) 67(6):800-806.

[76] Mutter, *Alzheimer Disease: Mercury as a Pathogenetic Factor and as a Moderator*, Neuroendocrinol Lett. 2004; 25(5):275-283 (Inorganic mercury, found in dental amalgam, may play a major role [in the pathogenesis of Alzheimer's Disease.])

[77] Roses AD and Saunders AM. *Apolipoprotein E genotyping as a diagnostic adjunct for Alzheimer's disease.* Int Psychogeriatr. 1997; 9 (Supp. 1):277–288 and 317–321.

clarify the reason. APO-E has 299 amino acids with different ratios of cysteine and arginine at position 112 and 158. APO-E2 has 2 cysteines, apo-E3 one cysteine and one arginine, and APO-E4 two arginines.[78] As arginine, unlike cysteine, lacks the sulphydryl (SH) groups to potentially bind bivalent metals such as mercury, lead, copper or zinc, it would be logical to suspect the possibility of increased metal accumulation in those chronically exposed individuals who had not inherited APO-E2. Godfrey 2003 found there was a statistically significant increase in adverse effects in those patients having APO-E4/4 and APO-E 3/4 where those patients were chronically exposed mercury. Godrey went on to explain why this occurs:

> According to Saunders, the underlying reason for the apo-E-associated differences in AD susceptibility remains a mystery. However, a logical biochemical explanation has been proposed by Pendergrass and Haley, based on the different amino-acid configurations of the three apo-E isomers and their potential relevance to mercury elimination. Only ε2 (with two cysteine -SH groups), and to a lesser extent ε3 (with one –SH group), are able to bind and remove mercury from the brain and cerebrospinal fluid. This would oppose accumulation of mercury which is reported to be causal for the unique brain lesions that typify the AD brain including neuro-fibrillary tangles.

Godfrey added:

> Another aspect of AD pathology is the evidence that enhanced mitochondrial damage occurs in AD and ε4 genotype. Mercury is very destructive at the mitochondrial level where catalase can demethylate organic mercury species into highly reactive inorganic mercury. Inorganic mercury is also an extremely potent enzyme inactivator. Furthermore, chronic micro-mercurial toxicity specifically from dental amalgam has been documented and successfully treated by removal of amalgam and medical detoxification in 796 patients.
>
> Still, not all research results agree with mercury's causal role in AD. Elevated mercury was not found in seven different regions of AD brains compared to controls. However, the "controls" had possessed three amalgam surfaces whereas the AD subjects had six, likely obscuring any differences. Saxe et al. reporting on the mental health of 129 nuns, found no difference between those with amalgam and controls. However, 72% of the controls had no posterior teeth, and the remainder had a mean of only three teeth. All 129 could, therefore, have had a similar previous amalgam history and the half-life of mercury in the brain is measured in decades. This paper's conclusions, published in a dental trade journal, are at variance with those of another paper in the same journal on risk factors affecting dentists' health. The authors identified 3 factors with equally

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[78] Brouwer DA., *Clinical chemistry of common Apoprotein isoforms. J Chromatography B Biomed Applic.* 1996; 678 (1):23–41.

high statistical values (i.e. $p < 0.001$), namely, a mercury spill in the dental office, manual amalgamation, and the dentists' own amalgam status.[79]

Wojcik's research (2006) supported a correlation between a genetic inability to eliminate mercury when the APO-E4 allele has been inherited and an increased incidence of common symptoms and signs of chronic mercury toxicity.[80] Thus the increased likelihood of AD in APO-E4 is almost certain to be because of exposure to mercury, already known to be a powerful neurotoxin. Wojcik 2006 stated:

> Two very important brain nucleotide binding proteins, tubulin and creatine kinase (CK), showed greatly diminished activity and nucleotide binding ability in the AD brain tissues versus age-matched control brain samples.[81] Both tubulin and CK are proteins that bind the nucleotides GTP (guanosine-5'-triphosphate) and ATP (adenosine-5'-triphosphate), respectively.
>
> After testing numerous heavy metals, we observed that, in the presence of EDTA, or other natural organic acid chelators, only Hg2+ mimicked the biochemical abnormalities observed for tubulin in the AD brain homogenates examined. This was first done by adding low amounts of Hg2+ and other toxic heavy metals to homogenates of normal brain tissue in the presence of various metal chelators.
>
> The observation was that Hg2+ at very low micromolar levels (≅ 1 micromolar) could rapidly and selectively disrupt the GTP or [32P]8N3GTP binding active-

Additional articles link mercury to Alzheimer's Disease.[82] [83] [84] [85] [86] [87] [88] [89] [90] [91] [92] [93] [94] [95] [96] [97] [98] [99] [100] [101] [102]

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[79] Godfrey ME, Wojcik DP, Krone CA., *Apolipoprotein E genotyping as a potential biomarker for mercury neurotoxicity.* J Alz Disease 2003; **5**:189–195.

[80] Wojcik,*et al.*, *Mercury toxicity Presenting as chronic fatigue, memory impairment and depression: Diagnosis, treatment, susceptibility, and outcomes in New Zealand general practice setting* (1994-2006) Neuro Endocrinol Lett 2006;27 (4):415-423.

[81] Khatoon S, *et al.*, *Aberrant GTP β-tubulin interaction in Alzheimer's Disease.* Annals of Neurology 1989;26:210–5. David S, Shoemaker M, Haley B. *Abnormal properties of creatine kinase in Alzheimer's Disease brain: correlation of reduced enzyme activity and active site photolabeling with aberrant cytosol-membrane partitioning.* Molecular Brain Research 1998;54:276–87. Duhr EF, Pendergrass JC, Slevin JT, Haley B. *HgEDTA complex inhibits GTP interactions with the E-Site of brain β-tubulin.* Toxicology and Applied Pharmacology 1993 Oct.;122(2):273–88.

[82] Ehmann, *et al.*, *Brain Trace Elements in Alzheimer's Disease*, Neurotoxicology, 7(1):195-206 (Spring 1986).

[83] Thompson, *et al.*, *Regional Brain Trace-element Studies in Alzheimer's Disease*, Neurotoxicology, 9(1):107 (Spring 1988).

[84] Vance, *Trace Element Imbalances in Hair and Nails of Alzheimer's Disease Patients*, Neurotoxicology, 9(2):197-208 (Summer 1988).

[85] Wenstrup, *et al., Trace Element Imbalances in Isolated Subcellular Fractions of Alzheimer's Disease Brains*, Brain Res, 12;533(1): 125-31 (Nov. 1990).

[86] Mutter, *Alzheimer Disease: Mercury as a Pathogenetic Factor and Apolipoprotein E as a Moderator*, Neuroendocrinol Lett. 2004; 25(5):275-283 ("Inorganic mercury (found in dental amalgam) may play a major role [in the pathogenesis of Alzheimer's Disease."]).

[87] Duhr, *et al., Hg sup 2+ induces GTP-tubulin interactions in rat brain similar to those observed in Alzheimer's disease*, 75th Annu. Meet. FASEB, Abstr. No 493, Georgia 21-25 April 1991.

[88] Ely, J.T.A, *et al.*, (1999) *Urine mercury in micromercurialism: bimodal distribution and diagnostic implications*. Bull Environ. Contam. Toxicol. 63:553-9.

[89] Haley, B., *Mercury toxicity: Genetic susceptibility and synergistic effects*. Medical Veritas 2 (2005) 535-542.

[90] Haley, B., *Relationship mercury to exacerbation Alzheimer's disease*. Medical Veritas 4 (2007) 1510-1524.

[91] Mutter, *et al., Amalgam Disease: Article by Gottwald et al.: Poisoning, allergy, or psychic disorder?* Int. J. Hyg. Environ. Health 204, 223-229 (2001).

[92] Olivieri, *et al., Mercury induces Cell Cytotoxicity and Oxidative Stress and Increase b-Amyloid Secretion and Tau Phosphorylation in SHSY5Y Neuroblastoma Cells*, Journal of Neurochemistry, Vol. 74, No. 1, 2000 231-236.

[93] Olivieri, *et al., The effects of beta-estradiol on SHSY5Y neuroblastoma cells during heavy metal induced oxidative stress, neurotoxicity and beta-amyloid secretion*, Neuroscience. 2002;113(4):849-55.

[94] Mutter, J., *et al.*; *Comments toxicology of Mercury and Chemical Compounds" by Clarkson and Magos* (2006) Critical Reviews in Toxicology, 37:537-549 (2007).

[95] Wojcik,*et al., Mercury toxicity presenting as chronic fatigue, memory impairment and depression: Diagnosis, treatment, susceptibility, and outcomes in New Zealand general practice setting*. (1994-2006) Neuro Endocrinol Lett 2006;27 (4):415-423.

[96] Pendergrass, J.C. and Haley, B.E., *Inhibition of Brain Tubulin-Guanosine 5'-Triphosphate Interactions by Mercury: Similarity to Observations in Alzheimer's Diseased Brain.* In Metal Ions in Biological Systems V34, Mercury and Its Effects on Environment and Biology, Chapter 16. Edited by H. Sigel and A. Sigel. Marcel Dekker, Inc. 270 Madison Ave., N.Y., N.Y. 10016 (1996).

[97] Pendergrass, J.C. and Haley, B.E., *Mercury-EDTA Complex Specifically Blocks Brain b-Tubulin-GTP Interactions: Similarity to Observations in Alzheimer"s Disease.* Status Quo and

With the weight of the evidence there can be little doubt that mercury more likely than not causes AD and certainly would exacerbate this disease. Certainly, FDA's Final Rule completely fails to address, much less refute, the concerns raised by this existing research.

NIH refuses to fund studies that may compromise its--and FDA's--long-held (but scientifically unsupported and unsupportable) claims touting the safety of amalgams, vaccines, and fluoride. Specifically, NIH has improvidently refused to consider mercury exposure as the cause of AD, This is done, in the opinion of many, to protect industrial interests in developing a drug to treat elevated beta-amyloid conditions. Perhaps in the near future, with help from international researchers, Alzheimer=s disease will be renamed, "mercury -induced dementia."

B. Parkinson's Disease

Scientific studies have suggested associations between mercury and neurological disease. These studies justify avoiding unnecessary mercury exposure. For example, one epidemiologic study correlates systemic mercury levels with increased risk of idiopathic Parkinson's Disease.[103] John Pearlman, M.D., reported that a 50 year-old athletic female patient had mercury/silver fillings removed and suddenly developed permanent neurological impairment that was ultimately

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Perspective of Amalgam and Other Dental Materials (International Symposium Proceedings at 98-105, (ed. by L. T. Friberg and G. N. Schrauzer.) Georg Thieme Verlag, Stuttgart-New York (1995).

[98] Pendergrass, J. C., Haley, B.E., Vimy, M. J., Winfield, S.A. and Lorscheider, F.L., *Mercury Vapor Inhalation Inhibits Binding of GTP to Tubulin in Rat Brain: Similarity to a Molecular Lesion in Alzheimer's Disease Brain.* Neurotoxicology 18(2), 315-324 (1997).

[99] David, S., Shoemaker, M., and Haley, B., *Abnormal Properties of Creatine kinase in Alzheimer's Disease Brain: Correlation of Reduced Enzyme Activity and Active Site Photolabeling with Aberrant Cytosol-Membrane Partitioning.* Molecular Brain Research accepted (1997).

[100] Hock C, *et al., Increased blood mercury levels in patients with Alzheimer's disease.* J Neural Transm. Vol. 23, No. 26. (1998) 105(1):59-68.

[101] Ely, J.T.A., *Mercury Induced Alzheimer's Disease: Accelerating Incidence?,* Bull Environ. Contam. Toxicol. (2001) 67:800-806.

[102] Duhr, E., *et al., HgEDTA Complex Inhibits GTP Interactions with the E-Site of Brain Beta-Tubulin,* Toxicology and Applied Pharmacology, 122, 273-280 (1993).

[103] Ngim, C., *Epidemiologic Study on the Association between Body Burden Mercury Level and Idiopathic Parkinson's Disease,* Neuroepidemiology, 8:128-141 (1989).

diagnosed as Parkinson's disease. She is now confined to a wheelchair.[104] Manufacturers of mercury/silver fillings warn that removal can be dangerous.[105]

C. Multiple Sclerosis

Multiple Sclerosis ("MS") was first commonly identified in the 19th century during the time in which mercury/silver fillings came into common use. In the early part of the twentieth century, MS was known as the "faker disease."[106] Unpublished anecdotal evidence indicates that a significant number of, but certainly not all, MS victims who have their mercury/silver fillings removed resolve (spontaneous remission) or improve gradually. By 1993, forty-two MS victims had filed adverse reaction reports with the FDA. Four of these were cured and twenty-nine improved. There is toxicological evidence that mercury poisoning victims (from sources other than fillings) and multiple sclerosis victims share similar symptoms. The *Encyclopedia of Occupational Health and Safety* discusses the symptoms of chronic mercury poisoning, in part, as follows:

> Nervous system involvement may occur with or without gastrointestinal symptoms, and may evolve in line with two main clinical pictures: (a) fine-intention tremor reminiscent of that encountered in persons suffering from multiple sclerosis.
>
> ***
>
> The most frequently encountered symptoms resemble those presented by persons with multiple sclerosis except there are no nystagmus and the two conditions have a different serology and different clinical courses.[107]

In 1966 Baasch concluded, based on sometimes severe neuroallergic reactions in acrodynia (pink disease) and his own observations of neurologic patients, that multiple sclerosis was an adult form of acrodynia (pink disease) and a neuroallergic reaction, in most cases, caused by mercury from amalgam fillings.[108] Baasch demonstrated in great detail that facts concerning

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[104] Smoking Teeth Interviews, http://www.youtube.com/watch?v=9ylnQ-T7oiA.

[105] DISPERSALLOY® DISPERSED PHASE ALLOY Tablets, Powder MATERIAL SAFETY DATA SHEET by Dentsply Caulk 38 West Clarke Avenue, Milford DE 19963-0359 Date prepared 9/20/95 Dated Revised 9/24/97.

[106] Scientific American, Sept. 1996, p. 25.

[107] Encyclopedia of Occupational Health and Safety, (3rd revised edition 1983). Parmeggiani, L., Technical Editor, pp. 1334-1335.

[108] Baasch, E., *Theoretische Ueberlegungen zur Aetiologie der Sclerosis multiplex. Die Multiple Sklerose eine Quecksilberallergie?* Schw. Arch. Neurol. Neurochir. Psychiat. 98, 1966, 1-18.

the geographical and age distribution, pathological development, and symptomatology of MS were all consistent with amalgams being the primary cause of the disease. He reported several specific cases and cited ongoing studies that showed cessation of progression and improvement of resolution of MS after removal of amalgam fillings.

In a very detailed study, Craelius in 1978 showed a strong correlation ($P<0.001$) between MS death rates and dental caries.[109] The data demonstrated the improbability that this correlation was due to chance. Numerous dietary factors were ruled out as contributing causes.

A hypothesis presented in 1983 by T. H. Ingalls, M.D.[110] proposed that slow, retrograde seepage of mercury from root canals or amalgam fillings may lead to multiple sclerosis in middle age. He proposed a correlation of unilateral multiple sclerosis symptomatology with ipsilateral amalgam-filled teeth. He also re-examined the extensive epidemiological data that show a linear correlation between death rates from MS and numbers of decayed, missing, and filled teeth. Ingalls[111] suggested that investigators studying the causes of MS should carefully examine the patients' dental histories. Furthermore, Dr. Ingalls' hypothesis included other environmental exposures to mercury. In 1986, he published data supporting his hypothesis that clearly demonstrate endemic clustering of MS in time and space over a 50-year time span that could be directly correlated to exposure to mercury.[112] Another study (Ahlrot-Westerlund 1987) found that multiple sclerosis patients had eight (8) times the normal level of mercury in their cerebral spinal fluid as compared to neurologically healthy controls.[113]

In a 1990 study, the University of Aarhus, Denmark, Department of Neurobiology, conducted an experiment in which three vervet monkeys received occlusal amalgam fillings, three others maxillary bone implants of amalgam, and three untreated monkeys served as controls, in order to trace possible accumulations of mercury. One year later, tissue sections from different organs were subjected to silver amplification by autometallography and analyzed at light and electron microscopial levels. It was found that amalgam fillings (total 0.7-1.2g) cause

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[109] Craelius, W., *Comparative epidemiology of multiple sclerosis and dental caries.* J. Epidemiol. Comm. Health 32:155-165 (1978).

[110] Ingalls, T.H., *Epidemiology, etiology, and prevention of multiple sclerosis.* Hypothesis and fact. Am. J. Forensic Med. Pathol. 4:55-61 (1983).

[111] Ingalls, T.H., *Triggers for multiple sclerosis.* Lancet, xx:160 (1986).

[112] Ingalls, T.H., *Endemic clustering of multiple sclerosis in time and place, 1934-1984.* Am. J. Forensic Med. Pathol. 71:3-8, (1986).

[113] Ahlrot-Westerlund, B., *Multiple Sclerosis and Mercury in Cerebrospinal Fluid.* Second Nordic Meeting on Trace Elements in Human Health and Disease. Odense, Denmark. 17-21 Aug 1987.

deposition of mercury in the following tissues: spinal ganglia, anterior pituitary, adrenal, medulla, liver, kidneys, lungs, and intestinal lymph glands. In the monkeys with maxillary silver amalgam implants (total .1-.3g), mercury was found in the same organs with the exception of the liver, lungs, and intestinal lymph glands. Organs from the three control animals were devoid of precipitate. These results strongly support what has been suggested previously-- that dental fillings in primates cause absorption of mercury released from amalgam fillings through the lungs and the intestinal tract, and that mercury is distributed to most organs and will eventually be found in the central nervous system. (The present data also show that silver released from the corroding filling is not absorbed.)

In a 1998 study, Dr. Svare and associates analyzed for its mercury content, the expired air of a group of 48 persons, 40 with and eight without dental amalgam restorations, before and after chewing[114]. Expired air samples were collected in polyethylene bags, and a known quantity of each was pumped into the mercury detector for measurement. The results showed that subjects with dental amalgams had higher pre-chewing mercury levels in their expired air than those without amalgams. After chewing, these levels were increased an average of 15.6-fold in the former and remained unchanged in the latter group. It was therefore concluded that *in situ* dental amalgams can indeed increase the level of mercury in expired air.

A paper written in 1994 by Dr. Siblerud of the Rocky Mountain Research Institute, Inc., investigated the hypothesis that mercury from silver dental fillings (amalgam) may be related to multiple sclerosis (MS).[115] It compared blood findings between MS subjects who had their amalgams removed to MS subjects with amalgams. MS subjects with amalgams were found to have significantly lower levels of red blood cells, hemoglobin and hematocrit compared to MS subjects with amalgam removal. Thyroxine levels were also significantly lower in the MS amalgam group and they had significantly lower levels of total T Lymphocytes and T-8 (CD8) suppressor cells. The MS amalgam group had significantly higher blood urea nitrogen and lower serum IgG. Hair mercury was significantly higher in the MS subjects compared to the non-MS control group. A health questionnaire found that MS subjects with amalgams had significantly more (33.7%) exacerbations during the past twelve months compared to the MS volunteers with amalgam removal.

An article developed by the MELISA Foundation in March of 2005, noted that MS is caused by the erosion of myelin, a substance which helps the brain send messages to the body. Metal particles entering the body can bind to this myelin. For those who are hypersensitive, this myelin-metal bond comes under attack from the immune system. In such cases, the progression of MS can be halted by removing the source of the metal. The role of myelin is one of the few facts on which those who study MS are able to agree. The MELISA Foundation has developed

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[55] Svare, C., *et al., The effect of dental amalgams on mercury levels in expired air.* J Dent Res 1981; 60:1668-1671.

[56] Siblerud, R.L., *et al., Evidence that mercury form silver dental fillings may be an etioogical factor in multiple sclerosis.* Sci Total Environ 1994 Mar 15;142(3):191-205.

what they believe is a breakthrough in understanding in MS: the link between metal allergy and the erosion of myelin[116]. They believe that they have also been able to prove that the myelin erosion can be halted if the source of the allergy is removed. Hypersensitive reactions are triggered by metal particles entering the body of a person allergic to the metal in question. These particles then bind to the myelin, slightly changing its protein structure. In hypersensitive people, the new structure (myelin plus metal particle) is falsely identified as a foreign invader and is attacked; an autoimmune response. Arrows point to the "myelin plaques" in the brain, common in patients with MS. Such plaques can be the result of metal allergy. Already, the MELISA Foundation has seen patients with MS make a partial, and, in some cases, a full recovery by removing the source of metal – often dental fillings.

Mercury has been documented to accumulate in the very areas of the nervous system from which most dramatic clinical symptoms of MS originate. Specifically, motor neurons accumulate more Hg than sensory neurons, and motor symptoms are seen to predominate over sensory symptoms in MS. Although more research needs to be done in this area, these results suggest dental mercury exposure from amalgams, as well as from any other chronic low-grade mercury exposure, must be given very serious consideration as possibly playing a role in the etiology of MS in such patients and more likely is the major cause of most MS. Genetic variability and individual ability to excrete mercury probably plays a role.[117]

In conclusion, the causation of MS is probably multi-factorial. Mercury is certainly one cause and probably the major cause of this disease.

D. Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS), more commonly known as Lou Gehrig's disease, is another "idiopathic" neurological disorder. ALS was first identified a few years after mercury/silver fillings came into common use. The clinical picture is quite interesting when considered in light of the documented neurotoxicity of mercury and the potential for neurotoxicity from mercury/silver fillings, often referred to as amalgam. Like MS, some people with ALS have found that their condition improved dramatically upon the removal of their amalgam fillings. Others have not improved which may be the result of poor technique resulting in high exposure to mercury during the removal process or they may be genetically a non-excreter of mercury. The correlation to mercury exposure was first suggested by Brown in 1954.[118]

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[116] Stejskal, *Role of Metals in Autoimmunity and Link to Neuroendocrinology*, Neuroendocrinology Letters 1999.

[117] Ely, *et al.*, *Urine Mercury in Micromercurialism: Bimodal Distribution and Diagnostic Implications*, Bull. Environ. Contam. Toxicol. (1999) 63:553-559.

[118] Brown, I.A., *Chronic Mercurialism, a cause of the clinical syndrome of amyotrophic lateral sclerosis*. AMA Arch. Neural Psych 72:674-681 (1954).

A 1961 study of eleven cases of chronic mercurialism from consumption of bread treated with a mercury-containing fungicide presented neurological symptoms akin to ALS with some more closely resembling progressive muscular atrophy. The paper concluded:

> 1. Since the same causative factor was operative in all these cases, it would appear that amyotrophic lateral sclerosis and progressive muscular atrophy are probably nosologically identical.
>
> 2. Amyotrophic lateral sclerosis should not be considered a disease entity but rather a syndrome of variable etiology.
>
> 3. ***Chronic mercurialism is a possible etiologic factor in amyotrophic lateral sclerosis."*** (emphasis added)" [119]

A 1978 report by Barber is also noteworthy. This involved two employees in a mercury oxide manufacturing plant who developed previously non-existent neurological symptoms resembling that of ALS.[120] An additional nineteen employees precipitously developed signs and symptoms which may be regarded as the early onset of a symptom complex of mercury intoxication that would likely have progressed to the ALS-like syndrome if the progression had not been interrupted by removal of the individuals from exposure to mercury. All symptoms, signs, and laboratory findings returned completely to normal after approximately three months in a mercury free work environment.

In 1983 the Journal of the American Medical Association reported of a 54-year-old man with symptoms resembling ALS after a brief but intense exposure to elemental mercury which resolved shortly thereafter, as his urinary mercury levels fell.[121] This man who had breathed mercury vapor while "salvaging the liquid mercury from industrial-grade thermometers" developed symptoms so similar to that of ALS that his neurologists gave him a "presumptive diagnosis of ALS." The man's physicians confirmed his exposure to mercury with a urine test "several weeks" after his exposure, which registered 99 micrograms of mercury per liter of urine, an alarmingly high concentration. Two months later, the man had recovered nearly completely. His "neurological findings were completely normal." His urine test indicated his mercury level had dropped to 29 micrograms, which is still much higher than the norm of 4 to 5 micrograms per liter. And "several weeks" later his mercury level had fallen to only 8 micrograms.

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[119] Kantarjian, A.D., *A syndrome clinically resembling amyotrophic lateral sclerosis following chronic mercurialism.* Neurology 11:639-44 (1961).

[120] Barber, T.E., *Inorganic mercury intoxication reminiscent of amyotrophic sclerosis.* J. Occupat. Med. 20:667-9 (1978).

[121] Adams, C.R., *et al., Mercury intoxication simulating amyotrophic lateral sclerosis.* J. Amer. Med. Assoc. 250:642-3 (1983).

A 1989 a Japanese study was done on ALS victims in the vicinity of the biggest mercury mine in Japan. That study found mercury at higher levels in ALS victims than in controls. They followed this with a study in 1990 which compared the mercury and selenium content in the hair of thirteen (13) ALS cases using neutron activated analysis and concluded that mercury with a low content of selenium might be one of the environmental factors.[122]

There are other studies indicating a connection between mercury and ALS,[123] a case report describing recoveries from ALS after the removal of mercury/silver fillings[124], and another case report of ALS developing after the accidental injection of mercury.[125] A 1990 study in the U.S. also involved neutron activated analysis of the brain, spinal cord, blood cells, serum, and nails of ALS victims compared to controls. Imbalances were detected in a number of trace and minor abundance elements in the tissue of ALS patients and more widespread changes were noted in the concentrations of mercury. The authors cautioned that the variation in mercury concentrations need not necessarily indicate active toxicity, as it could merely represent an enlarged pool of detoxified mercury or perhaps a labeling of a specific cellular ligand by mercury in ALS.[126]

Unlike MS there are not many adverse reaction reports to the FDA involving ALS and the removal of mercury silver fillings and it is very important to note there are individuals who have ALS and have never had mercury/silver fillings. So while mercury may be one cause of ALS as the foregoing suggests, it certainly is not the only one.

Despite this considerable evidence linking ALS and mercury, the NIH has refused to fund further research into mercury as a possible cause of this tragic disease which disables and--

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[122] Mano, Y., *Amyotrophic lateral sclerosis and mercury-preliminary report.* Department of Neurology, Nara Medical University. Rinsho Shinkeigaku Nov 1990, 30 (11) pl275-7, ISSN 0009-918X; Mano, *et al.*, *Mercury in hair of patients with ALS.* Rinsho Shinkeigaku July 1989, 29 (7) p844-8, ISSN 0009-918X.

[123] Haley, B., *et al.*, *GTP-binding proteins in amyotrophic lateral sclerosis cerebrospinal fluid.* Ann Neurol (1995).

[124] Redhe, P., *et al.*, *Recovery From Amyotrophic Lateral Sclerosis and From Allergy After Removal of Dental Amalgam Fillings.* Int J Risk Saf Medicine, 4:229-36 (1994).

[125] Schwarz, S., *et al., Amyotrophic lateral sclerosis after accidental injection of mercury.* J Neurol Neurosurg Psychiatry 1996 Jun;60(6):698.

[126] Khare, S.S., *et al., Trace element imbalances in amyotrophic lateral sclerosis,* Neurotoxicology, Vol. 11, No. 3, pages 521-532, 47 references (1990).

usually within two to five years-- kills five thousand Americans each year.

E. Severe Autism

A 2009 epidemiological study strongly associates prenatal mercury exposure from maternal dental amalgams with significantly increased rates of severe autism.[127] Holmes, *et al.*[128], found that mothers in the autistic group had significantly higher levels of mercury exposure through Rho D immunoglobulin injections and amalgam fillings than control mothers. Within the autistic group, hair mercury levels varied significantly across mildly, moderately, and severely autistic children, with mean group levels of 0.79, 0.46, and 0.21 ppm, respectively. Hair mercury levels among controls were significantly correlated with the number of the mothers' amalgam fillings and their fish consumption as well as exposure to mercury through childhood vaccines, correlations that were absent in the autistic group. Hair excretion patterns among autistic infants were significantly reduced relative to control. These data cast doubt on the efficacy of traditional hair analysis as a measure of total mercury exposure in a subset of the population. In light of the biological plausibility of mercury's role in neurodevelopmental disorders, this study provides further insight into one possible mechanism by which early mercury exposures could increase the risk of autism. [*See also*, Mutter J, Mercury and autism: Response to the letter of K. E. v. Muhlendahl, Int. J. Hyg. Environ. Health 208 (2005) ("Effective excretion of mercury will lead to higher hair, blood and urine mercury levels in a population that is being exposed to mercury at a constant, chronic, low level. The problem comes when those, who do not effectively excrete mercury, become exposed to a large dose, such as infants already exposed to mercury during pregnancy and who in addition received thimerosal containing hepatitis-B vaccines on the day of birth. The USA EPA set a standard of exposure on the safe level of ingested methyl mercury of 0.1 mg/kg body weight. Using this safety level, the newborn would have had to weigh 125 kg to take this exposure safely."); Haley B., *Mercury toxicity: Genetic susceptibility and synergistic effects*, Medical Veritas 2 (2005) 535–542 535 ("This data in Figure 2 show that normal children have birth hair levels of mercury that correlate with the number of amalgam fillings in the birth mother; whereas, in sharp contrast, the autistic children have exceptionally low levels of birth hair mercury, no matter what the number of amalgam fillings are found in the birth mother. This data strongly implies that autistic children represent a subset of the population that does not effectively excrete mercury from their cells.")]

F. Adverse Effects on Kidney Function

Mercury, we now know, concentrates in the kidneys, and experimental evidence shows that it can inhibit kidney function.[129] Distribution of mercury derived from dental amalgam to

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[127] Geier, D.A., *et al.*, *A Prospective Study of Prenatal Mercury Exposure from Maternal Dental Amalgams and Autism Severity*, Acta Neurogiol Exp (2009) 69:1-9.

[128] Holmes A.S. *et al*, *Reduced Levels of Mercury in First Baby Haircuts, of Autistic Children*, Int J Tox, 22:277–285, (2003).

[129] Boyd, N.D., *et al.*, *Mercury from dental "silver" tooth fillings impairs sheep kidney function.* American J. Physiol, 261 (RICP 30): R1010-4 (1991).

the kidney was demonstrated by Hahn, *et al.*[130] In this experiment, the organ that accumulated the greatest amount of mercury following amalgam placement was the kidneys.

Scientists are concluding that dental amalgam is an unsuitable restorative material because of its effects on the kidneys. "From the nephrotoxicity point of view, dental amalgam is an unsuitable filling material, as it may give rise to mercury toxicity. In these exposure conditions, renal damage is possible and may be assessed by urinary excretions of albumin, NAG, and gamma-GT."[131] Additional studies found harm to sheep's ability to clear inulin a measure of kidney function (black line) in just sixty days after implanting mercury/silver fillings.[132]

Critics of the sheep studies claimed that sheep chew too much. Similar studies were conducted on primates (monkeys) fed twice daily and the same distribution pattern for mercury was observed.[133] Animal studies demonstrate exposure to mercury vapor and autoimmunity.[134] One such study showed that dental silver amalgam and silver alloy implanted in the physiological milieu of the peritoneal cavity released enough metals to adversely affect the immune system.[135]

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[130] Hahn, L.J., *et al., Dental "silver" tooth fillings: a source of mercury exposure revealed by whole body scan and tissue analysis.* FASEB J, 3:2641-6 (1989).

[131] Mortada, W.L., *et al.*. Urology and Nephrology Center, Mansoura University, Faculty of Science, Egypt. J Nephrol 2002 Mar-Apr;15(2):171-6.

[132] Vimy, M.J., *et al., "Glomerular filtration impairment by mercury released from dental "silver" fillings in sheep."* Department of Medicine, Pathology, and Physiology, University of Calgary, Alberta, Canada. The Physiologist August 15 (1990).

[133] Hahn, L.J., *et al.,* Whole-body imaging of the distribution of mercury released from dental fillings into monkey tissues. FASEB, Vol. 4, Nov. 1990, pp. 3256-3260.

[134] Warfvinge, *et al., Systemic Autoimmunity Due to Mercury Vapor Exposure in Genetically Susceptible Mice: Dose-Response Studies.* Toxicol Appl Pharmacol, 132:299-309 (1995).

[135] Hultman, P., *et al., Adverse Immunological Effects and Autoimmunity Induced by Dental Amalgam and Alloy in Mice.* FASEB J, 8:1183-90 (1994).

Geier, *et al.*[136], reviewed the data sets taken from the Children's Amalgam Trial[137] and determined that overall, the present study using a different and more sensitive statistical model than the parent study, revealed a statistically significant dose-dependent correlation between cumulative exposure to Hg from amalgams and urinary glutathione-S-transferases, demonstrating damage to the proximal tubules of the kidney.

Likewise, Al-Saleh, *et al.*[138], demonstrated that exposure to the mercury from dental amalgam fillings had an adverse effect on kidney tubular functions in children, and that mercury-induced oxidative stress may have played a role in this mechanism.

G. Hearing Loss

The effects of amalgam dental fillings on auditory thresholds have been investigated. No significant correlation ($p>0.05$) was found between composite (non-amalgam) filling or drilling data and auditory thresholds. However, there was a significant positive linear correlation between amalgam fillings and auditory thresholds at 8, 11.2, 12.5, 14, and 16 kHz. The strongest association ($r=0.587$, $n=39$, $p<.001$, $r(2)=0.345$) was at 14 kHz, where each additional amalgam filling was associated with a 2.4 dB decline in hearing threshold (95% confidence interval [CI], 1.3-3.5 dB).[139]

H. Allergy to Mercury

In the Federal Registry, Volume 52(155):30089, August 12, 1987, the FDA changed the classification of dental mercury, a component part of mercury fillings, from the proposed Class II to Class I, stating, "...warnings under the misbranding provisions (21 U.S.C. 352) of the general controls of the act would warn dentists about the rare risk of allergic reactions among patients and the risk of toxicity to dental health professionals." Arriving at its conclusion that the risk of allergic reaction was "rare," the FDA relied on three (3) case reports, ignoring several other scientific studies clearly within the criteria set out in 21 C.F.R. 860.3, 860.7 for valid scientific evidence. These studies demonstrate that the risk of hypersensitivity (allergic) reaction to mercury effects at least five (5%) to eleven (11%) percent, and perhaps more, of those individuals receiving mercury fillings.

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[136] Geier, *et al.*, 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. Human and Experimental Toxicology 1–7 (2012).

[137] Woods JS, *et al.*, *Biomarkers of kidney integrity in children and adolescents with dental amalgam mercury exposure: findings from the Casa Pia children's amalgam trial.* Environ Res 2008; 108: 393–399.

[138] Al-Saleh, *et al., Effect of mercury (Hg) dental amalgam fillings on renal and oxidative stress biomarkers in children*, Science of the Total Environment 431 (2012) 188-196.

[139] Rothwell, J.,, *et al.,, Amalgam dental fillings and hearing loss.* Int J Audiol. 2008 Dec; 47(12):770-6.

The FDA's estimation that the risk of allergic reaction is "rare" is undocumented and unscientific. In fact, the scientific literature reflects that between 3.8% and 38.7% of the population with amalgams is allergic to mercury.[140] [141] [142] [143] These studies present formidable scientific documentation that a very significant percentage of our population is at risk for hypersensitive reactions to mercury derived from dental amalgam.

Since August 12, 1987 most manufacturers have failed to warn of the risk of allergic reaction as required by 21 U.S.C. § 352 and the FDA has failed to force them to do so under 21 U.S.C. 334 and 21 C.F.R. § 800.55. Despite acknowledging that a risk of allergy exists, FDA's Final Rule fails to take any steps to address this health risk.

I. Neurobehavioral Harm

Woods, *et al.*[144], recently determined that mercury derived from dental amalgam tooth fillings adversely affected neurobehavioral performance, particularly among boys with the CPOX4 polymorphism.

J. Other Adverse Effects

Research has linked mercury from fillings to periodontal disease, inflammation, and bone loss. In addition, research has linked mercury to idiopathic dilated cardiomyopathy (IDCM.)[145]

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[140] *See,* Djerassi, E., *et al.,* (1969) *The possibilities of allergic reactions from silver amalgam restorations.* Int Dent J 19:481-488, attached hereto as Exhibit 117. (None of controls had allergy to dental amalgam. Of 180 subjects, 16.1 % exhibited an allergic response to amalgam and 11 % were allergic to mercury. Of the subjects who had amalgam fillings for up to five years, 5.8 percent showed positive reactions. For subjects who had amalgam fillings for more than five years, 22.52 % had positive reactions.)

[141] North American Contact Dermatitis Group, *Epidemiology of Contact Dermatitis in North America*, Arch Dermatol, vol. 108, (Oct.1973), attached hereto as Exhibit 118. (5.0% reacted to ammoniated Hg; 8.0% reacted to thimerosal a mercury containing preservative.)

[142] White, R.R., *et al.,* (1976) *Development of mercury hypersensitivity among dental students*, J. Am Dent. Assoc. 92:1204-1207, attached hereto as Exhibit 119. (Authors patch-tested 396 dental students. Of those subjects having amalgam fillings for two years or less, 3.8 % had positive mercury patch tests, while 6.0% of those with amalgam fillings for more than five years were positive.)

[143] Miller, E.G, *et al.,* (1987) *Prevalence of mercury hypersensitivity in dental students.* J. Prosthet. Dent. 58:235-237 (Exhibit 120) (Authors tested 171 dental students and found a greater correlation to the number of amalgam fillings subjects had than to the length of time the fillings were in place. The percentage of the subjects testing positive to mercury ranged from 26.9% to 38.7% by class.)

[144] Woods, *et al., Modification of neurobehavioral effects of mercury by a genetic polymorphism of coproporphyrinogen oxidase in children*, Neurotoxicology and Teratology 34 (2012) 513–521.

Victims of this disorder may suffer cardiac arrest at an early age. Their hearts have 22,000 times more mercury than comparable hearts that suffered secondary cardiac dysfunction.

Snapp in 1981 carefully removed mercury/silver implants and his experimental subjects experienced a dramatic 90% decline in blood mercury to 10% of baseline.[146] The only logical conclusion is that their mercury/silver implants contributed substantially to their blood mercury. Snapp found a dramatic decline in blood mercury while Molin caused a dramatic increase followed by a slow drop in blood mercury over the next 12 months to 50% of baseline.[147] [148] The petitioners criticized the careless approach to mercury removal so when she repeated her study she provided adequate protections and confirmed Snapp's earlier finding.[149]

Other adverse health effects associated with mercury exposure are well-documented. Professor Matts Berlin, the World Health Organization's leading expert on the risks of mercury, recently concluded that: "Regarding the risk for retardation of brain development it is not according to science and standard of care to place amalgam fillings in children and fertile women."

Furthermore, there is no question that implanting mercury in teeth saturates jawbone and results in bone loss, produces inflammation and periodontal breakdown.[150] [151] [152] [153] [154] [155] Thus,

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[145] Frustaci, A., *et al., Marked elevation of myocardial trace elements in idiopathic dilated cardiomyopathy compared with secondary cardiac dysfunction.* J American College of Cardiology 33(6) 1578 (1999).

[146] Snapp, K.R., *et al., Contribution of Dental Amalgams to Blood Mercury Levels.* J Dent Res 65:311, 1981 Abstract #1276, Special issue.

[147] Molin, M., *Mercury Released from Dental Amalgam in Man*, Swedish Dental J. Supp. 71 1990.

[148] Molin, M., *Mercury, selenium, and glutathione peroxidase before and after amalgam removal in man.* Acta Odontol Scand 48:189-202 (1990).

[149] Molin, M., *Kinetics of mercury in blood and urine after amalgam removal.* J Dent Res 74:420 IADR Abstract 159 (1995).

[150] Zander H.A., *Effects of silicate cement and amalgam on the gingiva* JADA, Vol. 55:11-15 (1957), reported "materials used in restorative dentistry may be a contributing factor in gingival disease."

as early as 1973, it was apparent that the presence of dental mercury-amalgam resulted in chronic inflammation and bleeding in the gingival tissue adjacent to it; in other words, *in situ* amalgam produced chronic gingivitis.[156]

In 1984, the year of the NIDR/ADA Workshop, Fisher *et al.*,[157] reported that at amalgam sites alveolar bone loss was very pronounced and statistically significant as compared to control non-amalgam sites. In other words, *in situ* amalgam produces chronic periodontitis. Periodontal disease is the principle reason for two-thirds of adult tooth loss in the U.S. and mercury from tooth restorations contributes substantially to this common disease.

In 1995, an important review article summarizing some of the scientific documentation concerning dental amalgam was published in the highly prestigious scientific publication, the FASEB Journal. The authors detailed the scientific data and conclusions from scores of peer-reviewed articles documenting the deleterious effects of mercury vapor on the immune, renal, reproductive, and central nervous systems. The authors noted that "[r]esearch evidence does not support the notion of amalgam safety." In their conclusion, the authors admonished that:

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[151] App G. R., *Effect of Silicate, Amalgam, and Cast Gold on the Gingiva.* J. Prost Dent Vol. 11 #3 pp.522-532 (1961), suggested that there was greater chronic inflammation around amalgam sites than non-amalgam areas.

[152] Trott and Sherkat, J CDA, 30:766-770 (1964), demonstrated that the presence of amalgam correlates with gingival disease. Such disease was not present at contralateral amalgam-free sites.

[153] Sotres, L. S., *et al., A Histologic Study of Gingival Tissue Response to Amalgam, Silicate and Resin Restorations* J. Periodo. 140: 543-546 (1969), confirmed the Trott and Sherkat findings.

[154] Turgeon, *et al.*, (J CDA 37:255-256 (1972)) reported the presence of very significant erythema around amalgam restorations that was not present at control non-amalgam sites.

[155] Trivedi, S.C. and Talim, S.T. *The response of human gingiva to restorative materials,* J. Prosth. Dentistry, 29:73-81 (1973), demonstrated that 62.5% of amalgam sites have inflammatory periodontal tissue reaction.

[156] Goldschmidt, P.R. *et al., Effects of amalgam corrosion products on human cells.* J. Perio. Res., 11:108-115 (1976), demonstrated that amalgam corrosion products were cytotoxic to gingival cells at concentrations of 10-6; that is, micrograms/gram of tissue.

[157] Fisher, D., *et al., A 4-year follow-up study of alveolar bone height influenced by two dissimilar Class II amalg*am restorations Journal of Oral Rehabilitation Vol. 11, pp 399-405 (1984).

The collective results of numerous research investigations over the past decade clearly demonstrate that the continuous release of Hg° from dental amalgam tooth fillings provides the major contribution to Hg body burden. The experimental evidence indicates that amalgam Hg has the potential to induce cell or organ pathophysiology. At the very least, the traditional dental paradigm, that amalgam is a chemically stable tooth restorative material and that the release of Hg from this material is insignificant, is without foundation. One dental authority states that materials are presently available that are suitable alternatives to Hg fillings.

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It would seem that now is the time for dentistry to use composite (polymeric and ceramic) alternatives and discard the metal alchemy bestowed on its profession from a less enlightened era. Although human experimental evidence is incomplete at the present time, the recent medical research findings presented herein strongly contradict the unsubstantiated opinions pronounced by various dental associations and related trade organizations, who offer assurances of amalgam safety to dental personnel and their patients without providing hard scientific data, including animal, cellular and molecular evidence, to support their claims.[158]

VII. Conclusion

We certainly hope that the foregoing discussion is helpful to SCENIHR as it attempts to determine an appropriate reference dose for mercury. We are confident that any risk assessment that adheres to the published scientific principles of risk and exposure assessment will demonstrate that dental amalgam fillings are unsuitable for use as a tooth restorative material. Given the time constraints and the number of citations contained herein, we were able to forward most, but not all, of the publications cited herein. Should SCENIHR desire all of these publications and be willing to provide additional time, IAOMT will endeavor to forward all of these publications.

Sincerely yours,

Boyd E. Haley

Boyd E. Haley, Ph.D., Professor Emeritus
and past Chairman of the Chemistry Dept.,
University of Kentucky
IAOMT Scientific Advisory Board

Sincerely yours,

William E Virtue DDS

William E. Virtue, DDS, President
IAOMT

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[158] Lorscheider, F.L., *et al.*, *Mercury Exposure from Silver Tooth Fillings: Emerging Evidence Questions a Traditional Dental Paradigm.* FASEB J., 9:504-8 (1995).