PETITION FOR RECONSIDERATION

The Petitioners listed below submit this Petition for Reconsideration pursuant to 21 C.F.R. § 10.33, and hereby request that the Food & Drug Administration reconsider the classification of dental amalgam fillings into Class II per the FDA's August 4, 2009, Final Rule.

Via Hand-Delivery, this 3rd day of September 2009

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PETITION FOR RECONSIDERATION

The undersigned submits this petition for reconsideration of the decision of the Commissioner of Food and Drugs in Docket No. FDA-2008-N-0163**.**

A. DECISION INVOLVED:

FDA's August 4, 2009, Final Rule classifying dental amalgam in Class II and concomitant failure to prepare an Environmental Impact Statement, or at least, and Environmental Assessment under the National Environmental Protection Act ("NEPA.")

B. ACTION REQUESTED:

This Petition pertains to dental mercury capsules (hereinafter sometimes referred to as "mercury fillings" or "dental amalgam.") It is hereby requested that the Commissioner of the Food and Drug Administration ("FDA") take the following actions with respect to mercury fillings:

1. Formally ban the use of encapsulated mercury fillings as a dental restorative material pursuant to section 516 of the Medical Device Amendments of 1976 (21 U.S.C. 360f) and 21 C.F.R. 895. 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.

2. Alternatively, place encapsulated mercury fillings into Class III pursuant to section 513(3) of the Act (21 U.S.C. 360 c(e)) and 21 CFR 860, and seek strict proof of safety and effectiveness.

3. If the FDA decides to place encapsulated mercury fillings into Class III, FDA should place restrictions (not special controls) on the use of this material in young children, women and particularly women of childbearing age, males, patients with compromised kidney, immune, and neurological function, those who are hypersensitive to mercury, those who test positive for apolipoprotein E4 or coproporphyrinogen oxidase (CPOX4), and other persons within susceptible subpopulations as described herein. Neither "Class II controls" nor "Special Controls" can accomplish a reasonable assurance of safety for all sectors of our general population. Reasonable assurance of safety can only be achieved by abolishing the use dental amalgam or by placing it into Class III.

4. Under any of the foregoing alternatives, to require that an Environmental Impact Statement, or at least, an Environmental Assessment be prepared pursuant to 21 CFR 25.40 and NEPA.

C. STATEMENT OF GROUNDS:

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 explained its attempts to address the recommendations of the Joint Panels that convened in September 2006 and rejected the conclusions in the FDA White Paper on amalgam fillings.

Mercury fillings must be banned from the market [12 U.S.C. §360f] or classified in Class III. [12 U.S.C. §360c] These fillings are not safe and should be removed from the market, just

as every other mercurial medical device and substance has been. At the very least, they should be placed in Class III so that the amalgam manufacturers are required to prove that they are safe. 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, the FDA should ban mercury fillings as the predominant source of mercury exposure in the general population.

There are several obvious flaws in the FDA's Final Rule, as follows:

- FDA Final Rule on the classification of dental amalgam is based on a superficial and inadequate review of the literature.

- The estimated mercury vapor exposure from dental amalgam is incomplete, ill-composed, ill-conceived, indefensible, and inaccurate.

- An effective and defensible risk assessment for mercury vapor complies with EPA (2004, 1998, 1994) and the National Academy of Sciences (NAC, 2008).

- FDA fails to utilize a methodical analysis of the 'weight of evidence' of the toxicological literature.

- FDA offers no detailed quantitative analysis of its toxicological database leading to the determination of a defensible regulatory reference exposure level.

- FDA fails to utilize a methodical, transparent, and defensible quantification of exposure for comparison to that reference exposure level.

- FDA makes no defensible attempt to compare the full range of Hg° exposures across the entire amalgam-bearing U.S. population to regulatory reference exposure levels designed and intended to protect the general population.

- FDA only considers exposures attributed to a maximum of ten filled teeth, and only in adults, but incorrectly assumes this also applies to children six years and older.

- The FDA ignores children younger than six years, but children as young as three years receive amalgam fillings.

- The FDA ignores persons with more than ten amalgam fillings, but adults often have up to twenty-five (and possibly more) amalgam-filled teeth.

- The FDA makes no attempt to determine the number or percentage of Americans excluded from its risk assessment.

- The FDA omits to quantify the full range of Hg° exposure across the entire population, in all relevant age groups.

- The FDA omits to quantify the proportion of the amalgam-bearing population that exceeds the EPA RfC and the ATSDR MRL, the two reference exposure levels that purportedly provide health protection to the non-occupationally exposed general population.

- The FDA omits to quantify the exposure in children less than six years of age, an age group considered the most vulnerable to exposure and adverse effects and a population group that does, indeed, receive amalgam fillings.

- Many of the FDA calculations in the final rule are in error, in part due to improvident reliance on outdated or non-authoritative sources of information.

- FDA utilizes unreliable values for its assumed inhalation rate; FDA relies on EPA's RfC but inexplicably fails to recognize EPA (1997; 2008) as the most nationally and internationally authoritative information source on human inhalation rates.

- The RfC-associated dose and MRL-associated dose is improperly extrapolated to apply to children. These doses should only be derived for adults, the age group studied in the occupational studies upon which the RfC and MRL are based.

- FDA fails to adjust inhaled dose for the 80% absorption of mercury vapor in the lungs.

- FDA fails to standardize the internal doses associated with the RfC and MRL (and those from amalgam) to body weight due to the great disparity in body weights in the different age groups being considered.

- Contrary to the FDA's statement, the WHO Environmental Health Criteria 118 (WHO 1991) did not "[find] *that values generally in the range of 1-5 µg/day were estimated in the U.S. adult population*". Rather, 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).

- Contrary to FDA's assertion, the WHO (2003) did not conclude that "[t]he highest estimate that WHO reports was a dose of 12 µg/day, for middle-aged individuals with approximately 30 amalgam surfaces (Ref. 22)." In the Executive Summary of this document (WHO 2003), WHO clearly states "[d]ental 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.**"

- Based on FDA's method of estimating Hg° exposure from dental amalgam, and assuming that the RfC is derived correctly, the number of fillings necessary to exceed the RfC are:

    - Child 3-6 yrs – 2 fillings.
    - Child 6-11 yrs – 2 fillings.
    - Teen 12-19 yr – 3 fillings.
    - Adults – 7 fillings.

- Based on FDA's method of estimating Hg° exposure from amalgam, and assuming the MRL is derived correctly, the number of fillings that result in exceeding the MRL are:

    - Child 3-6 yrs – 2 fillings.
    - Child 6-11 yrs – 2 fillings.
    - Teen 12-19 yr – 4 fillings.
    - Adults – 5 fillings.

- The FDA has inadequately quantified Hg° exposure in, or totally omitted to consider, the following Americans:

    - 428,000 American toddlers aged three and four years that possess amalgam filled teeth, and 260,000 of these toddlers that would exceed the MRL-equivalent dose of mercury from their amalgam fillings, and 61,000 toddlers who would exceed the RfC-equivalent dose for mercury.

- 11,386,000 American children between the ages of five and eleven who may possess amalgam filled teeth, bearing from one to sixteen amalgam-filled teeth. Of these children, 5,909,000 would exceed the MRL-equivalent dose of mercury from their amalgam fillings, while 3,205,000 would exceed the RfC-equivalent dose for mercury vapor.

- 19,856,000 American teens between the age of twelve and nineteen who may possess between one and twenty-two filled teeth, for whom the FDA considered it unnecessary to quantify their precise mercury exposure from dental amalgam. Of these teens, 6,378,000 would exceed the MRL-equivalent dose of mercury from their amalgam fillings, while 2,965,000 would exceed the RfC-equivalent dose for mercury. Also in this age group, nearly three million would have more than ten filled teeth; in excess of the number of amalgam-filled teeth (and their associated dose and potential health effects) even considered by the FDA in their Final Rule.

- Up to 118 million adult Americans who may possess between one and twenty-five filled teeth. Of these, 43,550,000 would exceed the MRL-equivalent dose of mercury from their amalgam fillings, while 21,682,000 would exceed the RfC-equivalent dose for mercury. Also in this age group, nearly 44 million would have more than ten filled teeth; in excess of the number of amalgam-filled teeth (and their associated dose and potential health effects) even considered by the FDA in their Final Rule.

- In all, between the young age groups ignored in the FDA Final Rule, and those with more than ten filled teeth, also ignored in the FDA Final Rule, some 48 million Americans are omitted from consideration by the FDA.

- The FDA failed to recognize or rectify the inadequacy and non-valid nature of the EPA RfC or the ATSDR MRL:

    - The EPA categorizes mercury vapor as a neurotoxin but the RfC has not yet been revised and updated to comply with EPA's (1998) guidance on the assessment of neurotoxins nor the guidance provided by the National Academy of Sciences (NAS 2008).

- The EPA acknowledged as early as 2002 that significant new literature was available on the toxicity of mercury vapor; FDA cannot properly cite EPA's lack of action to revise the RfC and address the new literature as 'evidence' of the lack of new and significant studies.

- The reviews by EPA (1995) and the ATSDR (1999) are not recent, as indicated by FDA; the EPA RfC cites no literature later than 1995, now some fourteen years out-of-date. The most recently dated citation within the ATSDR Toxicological Profile on Mercury (ATSDR, 1999) is 1999, now some ten years out-of-date.

- FDA claims to have reviewed relevant literature up to July 2009, but it failed to locate Health Canada (2006), Richardson *et al*. (2009), Ratcliffe *et al*. (1996), among many other relevant studies and reports, discussed below.

- The FDA failed to recognize that studies of workers at chloralkali plants, where concomitant exposure to mercury vapor and chlorine gas occurs, are invalid for establishing reference exposures levels for non-occupational exposure to Hg°.

- Mercury has been identified in a large number of peer reviewed studies as being a likely causes of the more prevalent neurological disorders such as Alzheimer's Disease, severe autism, multiple sclerosis (ms), amyotrophic lateral sclerosis, and Parkinson's Disease. Mercury also causes hearing loss, periodontal disease, kidney dysfunction, and allergy.

- FDA failed to prepare an environmental impact study, or at least an environmental assessment, in violation of the National Environmental Protection Act.

1. Introduction

The FDA final rule on amalgam is based on a superficial review of the literature on the health effects of mercury vapor, and estimates of mercury vapor exposure from dental amalgam, both of which that are incomplete, ill-composed, ill-conceived and inaccurate. Although purporting to be a 'risk assessment', the documentation is nothing of the sort. 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 US EPA (2004, 1998, 1994) and most recently, by the US 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. All three of these critical steps are missing from the FDA final rule.

2. 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. However, the FDA only alludes to average or typical exposure levels, citing dated (predating 1993) reviews which they themselves only cite other yet older reviews.

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 US 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. Unfortunately, with respect to mercury vapor exposure from dental amalgam, the FDA never quantifies exposure in those members of the US population who are maximally exposed – those with up to twenty-five amalgam-filled teeth. The FDA only considers those with up to ten amalgam fillings.

Further, a defensible risk assessment does not exclude any segment of the US population. Unfortunately, the FDA never even attempted to quantify the mercury exposure in children under six years of age, despite it being known that children as young as 3 years of age do receive amalgam fillings and, as a result, are exposed to mercury vapor from this source. The significance of this oversight 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) was open and transparent about the prevalence of mercury fillings in the Canadian population, with adults having up to 25 filled teeth and children as young as 3 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 10 fillings, nor omitted to consider children less than 6 years of age. Both such considerations were omitted by the FDA in their final rule.

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

Although FDA appears to agree that reference air concentrations derived for the protection of the non-occupationally exposed, general population should be employed for the assessment of potential risks posed by amalgam (From FDA Final Rule: "*These reference values ... are considered to represent chronic or lifetime inhalation exposures that are free from adverse health outcomes and protective of human health for all individuals, including potentially sensitive populations such as children prenatally or postnatally exposed to mercury vapour.*"), the only comparisons the FDA presents relate to effects and exposure levels reported in

occupational studies of adults. There was no attempt to accurately quantify exposure to mercury vapor arising from the use of dental amalgam in the general US population, nor to compare those exposure levels to the reference air concentration (RfC) published by the US EPA (EPA, 1995) or the minimal risk level (MRL) published by the ATSDR (1999), both reference levels established for the protection of that non-occupationally exposed U.S. general population. 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.

4. How detailed and precise should exposure assessments be?

The lack of precision offered by FDA with respect to the average exposure to mercury from dental amalgam, not to mention their total failure to dependably quantify the range of exposure including those maximally exposed and those younger than six years of age, is disconcerting. The FDA has failed to adequately quantify:

- the full range of exposure across the entire population, in all relevant age groups;

- the proportion of the amalgam-bearing population that exceed the US EPA RfC and the ATSDR MRL, the two reference exposure levels identified by the FDA as providing health protection to the non-occupationally exposed general population;

- the exposure in children less than 6 years of age, an age group considered the most vulnerable to exposure and effects and a population group that does, indeed, receive amalgam fillings.

5. 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

a. Internal doses associated with the RfC and MRL

The FDA attempts to convert the RfC and MRL to an absorbed dose in their Final Rule, incorrectly estimating the following internal doses:

Age group	RfC-associated intake (µgs /day)	MRL-associated intake (µgs /day)
Adults	4.9	3.2
5 year old Children	2.3	1.5
1 year old Infants	1.7	1.2

However, in calculating these absorbed doses, the FDA makes four key errors.

- it uses unreliable values for inhalation rates;

- it fails 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;

b. Inhalation and Absorption Rates

Rather than accessing the most nationally and internationally authoritative data and information on inhalation rate – that compiled and thoroughly analyzed by the US EPA (1997; 2008) -- the FDA chose to estimate inhalation rates on the basis of only two citations. US 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. This is significantly less than FDA's undependable estimate of 16.2 m3/day.

The FDA acknowledges on page 8 of its Final Rule that the inhaled absorption rate for mercury vapor is 80%, yet it fails to apply this factor to its calculations in deriving the absorbed doses based on the RfC and MRL. Instead, FDA assumes 100% absorption of the inhaled mercury vapor. This error incorrectly pushes the permissible dose higher than is should be.

c. Standardization to Account for Varying Body Weights

In order to conduct any form of comparison of the FDA's assumed mercury vapor dose (1 to 5 µgs per seven to ten fillings) 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 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 US 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 (as assumed by the FDA in their Final Rule), 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.

6. Mercury Exposure from Dental Amalgam

The FDA cites an ill-defined and unsubstantiated estimate of absorbed mercury exposure from dental amalgam of 1 to 5 µgs/day that supposedly relates to the presence of between 7 and 10 amalgam fillings. This conclusion is attributed to a report by the Public Health Service published in 1993 (PHS, 1993). This cited report did not contain or conduct a detailed quantification of mercury exposure but based its estimates on the review of other yet older reports. In fact, PHS (1993) acknowledged that estimates of mercury exposure from amalgam span 1 µg/day to 29 µgs/day (see PHS, 1993, Appendix III), with higher estimates appropriately acknowledged for the sizable population of persons who have more than ten amalgam fillings.

Contrary to the FDA's statement, the WHO Environmental Health Criteria 118 (WHO 1991) did not "[find] *that values generally in the range of 1-5 µg/day were estimated in the U.S. adult population*". Rather, 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). Contrary to FDA's assertion, the WHO (2003) did not conclude that *"[t]he highest estimate that WHO reports was a dose of 12 µgs/day, for middle-aged individuals with approximately 30 amalgam surfaces (Ref. 22)*". 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.****"*

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

In order to conduct any form of comparison of the FDA's assumed mercury vapor dose (1 to 5 µgs per 7 to 10 fillings) 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 body weight/day.

If we assume, *arguendo*, that ten amalgam fillings deliver a daily dose of mercury of 5 µgs/day as an absorbed dose (per the FDA Final Rule), 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

Assuming FDA is correct in its estimate of dose associated with ten amalgam fillings, 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 assumed by the FDA to be 'safe.'

We have no doubt that FDA has the resources and expertise to properly assess the risks associated with dental amalgam. Sadly, FDA's clear priority is to defend at all costs the continued use of mercury in dentistry — even at the expense of the public health. It is not surprising, therefore, that FDA declined to validly and defensibly compare its estimate of the average or typical mercury vapor exposure to the very reference exposure levels it represents to be safe for the general population.

8. Assessing the Percentage of the Population Receiving Doses of Mercury that Exceed the RfC and the MRL

As previously stated, FDA relies on a report from 1993 (PHS, 1993) for quantification of mercury exposure from amalgam ranging between 1 and 5 µgs/day. However, that exposure level represents only the average exposure in adults, associated with possessing an average of

seven to ten amalgam-filled teeth. The FDA further assumes that this range of exposure occurs (and is safe) in children six years of age and older, as well as in adults. Given that the FDA final rule acknowledges that amalgam can be the single greatest source of exposure to mercury vapor in the U.S. population, it is astonishing that the FDA did not undertake a more quantitative and definitive analysis of exposure to mercury from amalgam, especially considering the billions of fillings placed in millions (10s to 100s) of Americans (statistics as described by FDA).

The other questions that FDA should have answered are:

1. Just how many American adults with amalgam fillings are receiving a dose greater than either the EPA RfC or the ATSDR MRL?

2. Just how many American children under six years of age with amalgam fillings are receiving a dose greater than either the EPA RfC or the ATSDR MRL?

These questions are answered below.

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. It is unfortunate that the FDA did not avail itself of that data. It is also unfortunate that the deadline for submission of this document to the FDA provides insufficient time for the Holistic Dental Association to obtain that same data. However, given the comparability of living standards between Canada and the US, we will apply available Canadian data for these derivations here, as they will be comparable to the dental care/dental health status in the U.S. population.

Based on data available from Health Canada (HC, 1995) on the proportion of various age groups bearing amalgam fillings, and 2009 US population census projections from the US Census Bureau (http://www.census.gov/popest/national/asrh/2008-nat-res.html) the following number of Americans with amalgam fillings are evident:

a. Up to 5.1% of American children aged 3 and 4 years of age may possess amalgam filled teeth, representing 428,000 American toddlers for whom the FDA considered it unnecessary to quantify their mercury exposure from dental amalgam. Of these toddlers, 260,000 would exceed the MRL-equivalent dose of mercury from their amalgam fillings, while 61,000 would exceed the RfC-equivalent dose for mercury.

b. Up to 40.4% of American children between the ages of 5 and 11 may possess amalgam-filled teeth, bearing from one to sixteen amalgam-filled teeth, representing 11,386,000 American children for whom the FDA considered it unnecessary to quantify their precise mercury exposure from dental amalgam. Of these children, 5,909,000 would exceed the MRL-

equivalent dose of mercury from their amalgam fillings, while 3,205,000 would exceed the RfC-equivalent dose for mercury.

c. Up to 59.3% of American teens between the age of 12 and 19 may possess between one and twenty-two filled teeth, representing 19,856,000 American teens for whom the FDA considered it unnecessary to quantify their precise mercury exposure from dental amalgam. Of these teens, 6,378,000 would exceed the MRL-equivalent dose of mercury from their amalgam fillings, while 2,965,000 would exceed the RfC-equivalent dose for mercury. Also in this age group, 9% (nearly 3 million American teens) have more than 10 filled teeth; in excess of the number of amalgam-filled teeth (and their associated dose and potential health effects) even considered by the FDA in their Final Rule.

d. Up to 52.8% of the adult American population may possess between one and twenty-five filled teeth, representing more than 118 million Americans for whom the FDA considered it unnecessary to quantify their precise mercury exposure from dental amalgam. Of these, 43,550,000 would exceed the MRL-equivalent dose of mercury from their amalgam fillings, while 21,682,000 would exceed the RfC-equivalent dose for mercury. Also in this age group, 19.5% (nearly 44 million Americans) have more than 10 filled teeth; in excess of the number of amalgam-filled teeth (and their associated dose and potential health effects) even considered by the FDA in their Final Rule.

e. In all, between the young age groups ignored in the FDA Final Rule, and those with more than ten filled teeth, also ignored in the FDA final Rule, some 48 million Americans are receiving doses of mercury solely derived from their mercury fillings that exceed the MRL and the RfC. FDA should be especially concerned about these conclusions in view of the additional environmental exposure to mercury that is occurring in this country. Laks[1] reports that the total exposure of the U.S. population to mercury is on the rise. "This study is the first to report that there is a rise in the mean blood I-Hg (defined as "blood inorganic mercury") detection and I-Hg concentration within the US population over time." Laks also reports that his study "indicates that I-Hg deposition within the human body is significantly associated with biomarkers for the main targets of chronic mercury exposure, deposition and effect: the liver, immune system, and pituitary. These correlations between chronic mercury exposure, I-Hg deposition, and biochemical profile markers for the targets of I-Hg deposition confirm strong links between exposure and associated disease." FDA's Final Rule does not take into account this documented additional mercury derived from environmental (non-amalgam) sources and then compare that total mercury burden to the RfC and the MRL. Clearly, FDA's analysis fails to offer a reasonable assurance of safety for a substantial portion of the U.S. population.

9. Are the RfC and the MRL for Mercury Vapor Based on Current Knowledge?[2]

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[1] Laks, D.R., *Assessment of chronic mercury exposure within the U.S. population, National Health and Nutrition Examination Survey, 1999-2006*, Biometals, (Aug. 2009).

[2] 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.

a. The RfC and MRL are Outdated

The FDA incorrectly states that: "[the RfC and the MRL] *are considered to represent chronic or lifetime inhalation exposures that are free from adverse health outcomes and protective of human health for all individuals, including potentially sensitive populations such as children prenatally or postnatally exposed to mercury vapour."* Castorina and Woodruff (2003)[3] clearly demonstrate that*:* "Although noncancer outcomes may in some instances be reversible and considered less severe than cancer, our findings call into question the assumption that established RfD and RfC values represent negligibly small risk levels*."*

The EPA recognizes that mercury vapor is a neurotoxin. As such, the toxicological assessment by EPA of mercury and derivation of a suitable reference air concentration (RfC) must comply with EPA's (1998) guidance on the assessment of neutotoxins. The publication of that EPA guidance occurred three years after the publication of EPA's RfC for mercury vapor, thus indicating that this RfC is out of compliance with EPA's own policies and procedures for the assessment of neurotoxins. It is apparent, therefore, that this RfC is out of date and will eventually be (must be) updated to accurately reflect both the latest literature on mercury vapor toxicity and EPA's own neurotoxin risk assessment guidance.

The FDA incorrectly cites the EPA documentation associated with the out-of-date EPA RfC. The FDA allege that a 2002 contractor's report (screening assessment), prepared for the US EPA on toxicological studies of mercury vapor published between approximately 1995 and 2002, is evidence that the EPA found no new data or information warranting revision of the EPA RfC of 0.3 ug/m3. In fact, this is specifically contradicted by the EPA in the very citation referred to by the FDA:

> "A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfC for Mercury, elemental conducted in September 2002 ***identified one or more significant new studies***" [emphasis added] (see statement on "Screening-Level Literature Review Findings", Section I.B.6, of the EPA IRIS listing on elemental mercury (http://www.epa.gov/ncea/iris/subst/0370.htm)).

Although it is apparent that the EPA has yet to consider these new studies with respect to revising or updating its RfC, this inaction by EPA cannot be properly cited by the FDA as 'evidence' of a dearth of new and relevant studies. The EPA RfC was first published in 1995 (see http://www.epa.gov/ncea/iris/subst/0370.htm) and has not been updated for new toxicological studies since that time. In fact, contrary to the supposition of the FDA, the most recent study cited by the US EPA in support of its RfC is 1995.

FDA states that the EPA (1995) and ATSDR (1999) constitute 'recent' reviews of the toxicological literature on mercury vapor. This is, in fact, incorrect. As previously mentioned,

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[3] Castorina, R., *et al*., *Assessment of Potential Risk Levels Associated with U.S. Environmental Protection Agency Reference Values*, Environmental Health Perspectives, vol. 111, no. 10 (August 2003).

the EPA RfC cites no literature later than 1995, now some fourteen years out-of-date. The most recently dated citation within the ATSDR Toxicological Profile on Mercury (ATSDR, 1999) is 1999, now some 10 years out-of-date.

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).[4] If FDA had undertaken a thorough and effective review of all literature up to July 2009, as reported in their Final Rule, the Richardson, *et al* paper would have been identified. This is particularly true since the Richardson, *et al* paper is published in the journal *Regulatory Toxicology and Pharmacology*, a significant journal with high respect paid by the national and international regulatory community dealing with chemical exposures, such as mercury from dental amalgam.

It is also standard practice among practitioners of risk assessment to contact relevant national and international environmental health regulatory agencies to inquire of relevant unpublished reviews and documents. Had the FDA or their contractors followed that standard practice and contacted Health Canada to inquire about any relevant information, they would have been informed about both the document on mercury vapor and the subsequent journal publication. In fact, had the FDA or their contractors simply done an internet search of Health Canada's various web pages, they would have discovered three key reports listed at: http://www.hc-sc.gc.ca/ewh-semt/contamsite/res/proj_pubs_journal-eng.php; three reports employed in Health Canada's development of an up-to-date reference exposure level for mercury vapor in the general population. It is also surprising that the FDA makes no mention of Health Canada's up-to-date REL (analogous to EPA's RfC) for mercury vapor of 0.06 ug/m3, some five times lower than the out-of-date EPA RfC of 0.3 ug/m3, and more than three times lower than the ATDSR's out-of-date MRL for mercury vapor of 0.2 ug/m3.

In a review by Ratcliffe, *et al.* (1996), a series of criteria were developed to critically evaluate available epidemiological, occupational and toxicological studies of Hg^0, towards determining if post-1980s studies provided evidence to warrant revision of the REL for Hg^0. That review found several studies that were positive for sub-clinical impairment of the CNS. The study of Fawer *et al*. (1983), the primary basis of all existing REL values, did not meet the criteria on study quality established by Ratcliffe, *et al*.

Ratcliffe, *et al*. did not restrict their evaluation to studies of neurotoxicity. They also identified a variety of studies that were positive or suggestive of sub-clinical nephrotoxic effects, occurring in the same general dose range associated with sub-clinical CNS effects. Additional recent studies have also identified nephrotoxic, neurotoxic and immunotoxic effects associated with Hg^0 exposure, reported at doses or exposure levels at or lower than the exposure levels associated with the Fawer study. As a result of the development of these factors, confidence in the current reference levels for Hg^0 is low, at least outside of FDA, and an evaluation of recent toxicological, epidemiological and occupational studies investigating neurologic, nephrologic and immunologic effects, conducted since 1995, is necessary.

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[4] 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).

This was recognized by the EPA which, in 2002, appended to their IRIS summary on elemental mercury (mercury vapor) the following statement:

> *Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfC for Mercury, elemental conducted in September 2002* ***identified one or more significant new studies.*** [Emphasis added]

These more recent studies have most recently been reviewed and evaluated by Health Canada (2006; *see also* Richardson *et al*., 2009).

b. The Fawer Study, Relied on by Both EPA and ATSDR, is a Study of Chloralkali Workers and not Appropriate for RfC or MRL Derivation

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. Hg2+ (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 Hg0 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 Hg2+, 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.

c. 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:

i. 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.

Several authors have indicated that gender is an important factor in the metabolic and toxicologic response to exposure to chemicals (Calabrese, 1986; Silvaggio and Mattison, 1994; Gochfeld, 1997; Iyaniwura, 2004). There is evidence that males and females respond differently to Hg° exposure, in terms of uptake, distribution, and toxicity. As discussed below, studies examining both genders have exhibited differing accumulation patterns in males and females, and faster elimination rates in males. These differences may result in variable, gender-related toxic response to Hg° exposure. The available data, however, are limited and inadequate to reliably quantify gender-related differences in toxicity.

It should be noted that both organic (methyl Hg) and inorganic forms of Hg were considered in this review of gender-specific response because once across the blood-brain barrier the ultimate biochemical fate of the ionic Hg moiety (Hg^{2+} from organic and inorganic Hg) is

identical (Lorscheider *et al*., 1995). FDA completely fails to account for this additional body burden when comparing exposure to the RfC and MRL.

Hongo *et al*. (1994) examined urinary Hg excretion by university staff and students who were occasionally exposed to Hg° vapor over a period of six years. Regression analysis indicated that the Hg° vapor exposure level was the major variable predicting urinary Hg excretion, but gender (along with age and the presence of amalgam fillings) was also reported to be an important factor. They did not, however, specifically quantify the gender-related differences.

Jokstad (1990) surveyed the Norwegian Dental Association to assess the significance of potential sources of Hg exposure. Urinary Hg excretion values were correlated to answers on the survey. In addition to correlations between environment and practice characteristics and Hg excretion values, the data indicated that urinary Hg excretion might be gender-dependent, due to the fact that the mean UHg levels of 849 participants were slightly lower in women compared to men (40 nmol/L versus 44 nmol/L). When a group of female assistants with higher exposures were excluded from the analysis, the average UHg concentration for women dropped to 38 nmol/L. The authors reported, "[n]either the length of work experience, nor the years in the current office facility correlate[d] with the urinary Hg levels." While there was a correlation between UHg concentrations and the number of hours spent per week in the clinic for the entire group and for the male participants, this correlation was not observed when female participants were evaluated alone. The mean Hg concentrations for females remained relatively constant and, for the most part, were lower than those measured in the male participants, especially at the higher exposure levels. The authors did not offer a definitive conclusion as to whether their results support gender-dependency in absorption or excretion.

At an annual American Dental Association (ADA) meeting, Kaste, *et al*. (1992) presented a study of dentists and dental assistants who had been evaluated for Hg exposure. Over 4000 participants (7.6% women) answered questionnaires and provided urine samples. There was a small difference in average UHg concentration (4.9 μg/L in women and 6.3 μg/L in men). This variation might, however, be attributable to the number of years of exposure as Kaste, *et al*. (1992) reported an average of 8.2 years in practice for the female participants and an average of 19.2 years in practice for the males.

Pamphlett, *et al*. (1997) compared the uptake of inorganic Hg by motor neurons in male and female mice and measured Hg concentrations in their kidneys. Significantly more neurons contained Hg granules in female mice than in male mice, and kidneys of male mice had significantly higher amounts of Hg when compared to the females. Pamphlett *et al*. (1997) concluded that the decreased deposition of Hg in the kidneys of the female mice resulted in an increase in circulating Hg, which was available for neuron uptake.

Pamphlett & Coote (1998) were interested in identifying the lowest dose of Hg vapor that resulted in Hg deposition in neurons, and in determining if female neurons were more susceptible to Hg vapor toxicity than male neurons. After a 50 $\mu g/m^3$ dose, Hg was observed in the spinal motor neurons of female mice at half the exposure time (6 hours) necessary for it to be observed in the spinal motor neurons of male mice (12 hours).

Nielsen & Anderson (1990) investigated the effects of different dose levels and routes of administration on whole body retention and relative organ distribution of Hg chloride in two strains of female mice. In addition, the authors investigated gender differences in the distribution of Hg chloride by comparing their results to a previous study with male mice (Nielsen & Andersen, 1989). This comparison showed that similar fractions of Hg body burden were distributed in the liver of males and females, while a significantly larger fraction of Hg body burden was deposited in the kidneys of the male mice than in female mice.

Thomas, *et al*. (1986) examined the integrated exposures of tissues of female and male rats to organic and inorganic Hg. While whole body comparisons indicated that integrated exposures of males and females to inorganic Hg were equal, this study demonstrated that the integrated exposure of the brain of female rats to inorganic Hg was 2.19 times that of the males. This finding suggested that there was a gender-related difference in the accumulation and/or retention of inorganic Hg in the central nervous system.

Miettnen (1973 as cited in Thomas, *et al*. 1986) reported that, in humans, the whole body half time for Hg elimination following ingestion of protein bound Hg chloride was faster in females than in males.

Hirayama & Yasutake (1986) and Yasutake & Hirayama (1988) studied C57BL/6N and BALB/cA mice to evaluate the mechanisms for gender-related differences in the *in vivo* fate of methyl Hg. A single administration of methyl Hg chloride in mature mice resulted in higher levels of Hg in urine of males than of females. Five minutes after exposure, Hg levels in male kidneys were higher than in female kidneys and these higher male concentrations were still in evidence after 24 hours. Lower Hg values were reported in other tissues of males when compared with females. After 24 hours, the Hg levels in urine were 6.5 times higher in males than in females. The levels of Hg in kidneys for males were higher than in females whereas the females had higher Hg levels in the brain, liver and plasma. Castrated males had Hg tissue levels similar to females except in the brain and castrated females exhibited decreased urinary excretion of Hg. The authors concluded, "tissue distribution and urinary excretion of the administered methyl Hg seem to be subject to sex hormone control. This study demonstrates that the metabolism and elimination of methyl Hg occur significantly faster in males and that the sequence of events leading to urinary excretion of methyl Hg may proceed under the control of sex hormones."

Magos *et al*. (1981) compared the sensitivity of female and male rats to methyl Hg. "After identical doses the brains of females always contained more Hg than those of males. Female rats developed more intensive co-ordination disorders and after five doses they had more extensive damage in the granular layer of the cerebellum than males." However, the regional distribution of Hg within the brain was the same in males and females. The elimination rate in male kidneys was found to be significantly faster (16 day half-life) than the elimination rate for female kidneys (37 day half-life).

Nielsen and Andersen (1991) found the route of methyl Hg administration did not affect the whole-body retention of Hg significantly but that female mice retained more Hg than did male mice. Kidney deposition in males was twice that in females, and the male mice excreted Hg significantly faster than did the females.

ii. Genetic predisposition to Hg toxicity

A variety of studies in animals (Aten, *et al*., 1992; Druet, *et al*., 1978; Hirszel, *et al*., 1985; Hultman and Enestrom, 1992; Matsuo, *et al*., 1987; Michaelson, *et al*., 1985; Pelletier, *et al*., 1990; Pusey, *et al*., 1990; Roman-Franco, *et al*., 1978; van der Meide, *et al*., 1993) (*see* reviews by Silbergeld, *et al*., 2005; Nielson & Hultman, 2002; ATSDR, 1999) demonstrate the occurrence of autoimmune glomerulonephritis upon exposure to Hg° in genetically susceptible animals.

Autoimmune glomerulonephritis results in observed proteinuria as a result of autoantibodies reacting with renal tissues. Some human evidence supports the existence of an immunologically mediated renal impact of Hg°, with deposition of IgG, immune complexes and/or complement C3 along the glomerular basement membrane (Lindqvist, *et al*., 1974; Tubbs, *et al*., 1982). This has been interpreted as evidence of a potential genetic predisposition to immunologically mediated renal response to Hg exposure, although the existence of a genetic polymorphism coding for the requisite genetic susceptibility has not been reported.

Echeverria, *et al*., (Echeverria, *et al*., 2006, 2005; Woods, *et al*., 2005; Heyer, *et al*., 2004) have recently identified polymorphisms in genes encoding for brain-derived neurotrophic factor (BDNF). Various detriments in neurobehavioural performance (Echeverria, *et al*., 2006, 2005) and in symptoms and mood (Heyer, *et al*., 2004) 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 neurobehavioural 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)) has also been observed and is associated with detriments in neurobehavioural response independent of Hg exposure. As with BDNF, the influence of the CPOX4 polymorphism and Hg exposure appeared to be additive.

iii. Fetal Effects of Mercury

Although a number of studies have identified dose-dependent increases in fetal brain Hg concentrations, dose–response data related to fetal neurotoxicity are non-existent with the exception of a single study (Morgan, *et al*., 2002) that reported a no-effect-level of 108.5 ng Hg/fetus (whole body) in rats. As a result, the potential for fetal exposure and effects must be considered in REL development, but at present must be addressed as a limitation of the database available for the determination of a REL for Hg°.

The uptake and distribution of Hg in the fetus following maternal exposure has been extensively reviewed (ATSDR, 1999; WHO, 2003). Animal studies suggest that the CNS is sensitive to prenatal Hg° exposure. However, clear dose–response data in relation to maternal

inhalation exposure to Hg° is lacking. In addition, available data relate to Hg° air concentrations two to three orders of magnitude greater than that generally encountered in the non-occupational environment. High quality epidemiological data (*e.g.*, with good exposure data and control of confounding factors) is lacking concerning the potential for CNS effects in children exposed in utero. Therefore, while there is evidence to demonstrate that fetal exposure does occur, and to suggest potential concern for fetal neurobehavioural effects following maternal inhalation exposure to Hg°, data are lacking to quantify potential risks.

As Hg° can readily cross the placenta (WHO, 2003), fetal exposure represents a concern in association with the inhalation of Hg0 by pregnant women (WHO, 1991; Drasch, *et al*., 1994; Yang, *et al*., 1997; Vimy, *et al*., 1990; Yoshida, *et al*., 1986, 1990). No hepatic or renal effects have been noted as a result of in utero exposure despite the fact that the liver and kidney accumulate the highest levels of Hg in the fetus (Drasch, *et al*., 1994; Morgan, *et al*., 2002; Yoshida, 2002; Yoshida, *et al*., 2002). A number of recent studies have examined the effects due to in utero exposure to Hg and have pointed to potentially irreversible neurological effects as the key concern (Ramirez. *et al*., 2003). This highlights the sensitivity of the developing CNS to Hg, with one author attributing this sensitivity to Hg's slow elimination from these tissues (Yoshida *et al*.,1999).

There have been a few studies published since the previously cited reviews were completed. Yoshida, *et al*. (2005) repeatedly exposed pregnant mice of metallothionein (MT)-null and wildtype strains to Hg^0 at concentrations of 0.5 mg/m3 and 0.56 mg/m3, respectively, for 6 h/day from gestational day (GD) 1 through 18.

Hg concentrations in the brain and kidney in the offspring were found to be significantly higher in the exposed groups (MT-null and wildtype) than in the controls. In the brain, Hg concentrations in the exposed males were not significantly different between the two strains, but the exposed MT-null females had significantly higher levels of Hg than the wildtype females. A histological examination did not reveal any abnormalities in the nerve tissues of the exposed mice regardless of strain or sex of the offspring.

Hg-exposed MT-null mice exhibited a significant decrease in total locomotor activity in males, and a learning disability in the passive avoidance response and a retarded acquisition in the Morris water maze in females, as compared with the controls. The authors concluded that MT may play a protective role for neurological effects associated with in utero Hg exposure, with its influence being more pronounced in females.

Another recent study examined the disposition and toxicity of inhaled Hg° in rats and the potential adverse effects on reproductive outcomes (Morgan, *et al*., 2002). Rats were exposed to 0, 1, 2, 4 or 8 mg Hg/m3 for 2 h/day from GD 6 through 15. Maternal toxicity was noted in the 4 and 8 mg Hg/m3 groups, which was characterized as a concentration-related decrease in body weight gain and mild nephrotoxicity. The accumulation of Hg in fetuses was found to be dose-dependent, however, no statistically significant effects on fetal brain weights or on fetal body weights were noted even with fetal Hg concentrations being noted to reach a mean of 108.8 ng Hg/fetus (whole body) on GD 10 (the only day on which whole body burden was examined) and 1.93 ng/brain by GD 15. The authors also noted a dose-related increase in levels of Hg in the fetal brain. While no effects were noted in the offspring following in utero exposure, a significant increase in the number of resorptions was noted in the highest dose group, where maternal

toxicity was observed. In the same dose group, post-natal litter size and body weights of neonates were significantly less than controls. The direct maternal toxicity reported at this exposure level confounds the interpretation of effects on reproductive outcomes.

A recent study in humans examined the presence and levels of total Hg in chord blood and meconium as an indicator of prenatal exposure and the potential for neurodevelopmental effects (examined using cognitive adaptive tests and clinical linguistic auditory milestone scale—CATS/CLAMS) (Ramirez, *et al.*, 2003). The authors did not provide details concerning the source of the exposures to Hg (both elemental and methyl Hg) in the study, but noted that there was likely some exposure to methyl Hg via the diet due to the consumption of fish. The study reported that Hg levels in hair and cord blood were negatively correlated with CATS/CLAMS results in both the control and exposed groups at two years of age. However, those exposed also had documented indicators of Hg presence at birth (presence of Hg in the meconium) and, therefore, the authors suggested that prenatal exposure, and not necessarily current exposure to Hg in children (*e.g.*, birth to two years of age), was the cause of the observed neurodevelopmental effects. While this study suggests that in utero exposure may result in neurological effects, these results should be interpreted with caution, as the authors did not control for confounding variables, such as concomitant exposure to other neurotoxicants and nutritional deficiencies.

10. 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

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[5] 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).[6] The elevated Hg imbalance in AD brain was confirmed in a follow up studies by Thompson and others (1998).[7] Through cell fractionation, Wenstrup was able to trace the accumulation of mercury into the cell organelle called the mitochondria (1990).[8] 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).[9] 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 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.

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

[6] 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).

[7] 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).

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

[9] 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.

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).[10]

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.[11] 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. [12] 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.[13] Professor Boyd Haley concluded in 2003 that Amercury and other blood-brain permeable toxicants that have enhanced specificity for 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.@[14] The demonstrated toxic synergy of mercury with other heavy metals is a concept completely omitted from consideration in FDA's Final Rule.

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[10] 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.

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

[12] 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.

[13] 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).

[14] 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).

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.[15] 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 4 million soles to 14 million soles based upon population age alone.[16] 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.[17] 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.[18] Several subsequent papers failed to 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.[19] 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:

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

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

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

[18] 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.

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

> 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 high statistical values (i.e. $p < 0.001$), namely, a mercury spill in the dental office, manual amalgamation, and the dentists' own amalgam status.[20]

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.[21] 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:

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

[21] 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.

> 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.[22] 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 ($\cong 1$ micromolar) could rapidly and selectively disrupt the GTP or [32P]8N3GTP binding active-

Additional articles link mercury to Alzheimer's Disease.[23] [24] [25] [26] [27] [28] [29] [30] [31] [32] [33] [34] [35] [36] [37] [38] [39] [40] [41] [42] [43]

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[22] 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.

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

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

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

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

[27] 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."]).

[28] 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.

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

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

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

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

[33] 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.

[34] 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.

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

[36] 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.

[37] 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).

[38] 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 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).

[39] 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).

[40] 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).

[41] 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.

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

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.[44] 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 diagnosed as Parkinson's disease. She is now confined to a wheelchair.[45] Manufacturers of mercury/silver fillings warn that removal can be dangerous.[46]

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."[47] 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:

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[43] 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).

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

[45] Smoking Teeth Interviews. DVD furnished FDA Joint Panels in 2006.

[46] 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.

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

> 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.[48]

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.[49] Baasch demonstrated in great detail that facts concerning 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.[50] 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.[51] 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[52] 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.[53] Another study (Ahlrot-Westerlund 1987) found that

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

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

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

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

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

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

multiple sclerosis patients had eight (8) times the normal level of mercury in their cerebral spinal fluid as compared to neurologically healthy controls.[54]

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 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[55]. 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).[56] 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

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[54] 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.

[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.

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 what they believe is a breakthrough in understanding in MS: the link between metal allergy and the erosion of myelin[57]. 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.[58]

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-

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

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

excreter of mercury. The correlation to mercury exposure was first suggested by Brown in 1954.[59]

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)" [60]

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.[61] 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.[62] 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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[59] Brown, I.A., *Chronic Mercurialism, a cause of the clinical syndrome of amyotrophic lateral sclerosis*. AMA Arch. Neural Psych 72:674-681 (1954).

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

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

[62] 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.[63]

There are other studies indicating a connection between mercury and ALS,[64] a case report describing recoveries from ALS after the removal of mercury/silver fillings[65], and another case report of ALS developing after the accidental injection of mercury.[66] 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.[67]

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--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

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[63] 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.

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

[65] 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).

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

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

maternal dental amalgams with significantly increased rates of severe autism.[68] Proclaiming human fetal safety based on minimal animal data, FDA inexplicably fails to explain how this important study eluded FDA's attention.

Holmes, *et al*.[69], 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.")]

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[68] 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.

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

f. Adverse Effects on Kidney Function

Mercury, we now know, concentrates in the kidneys, and experimental evidence shows that it can inhibit kidney function.[70] Distribution of mercury derived from dental amalgam to the kidney was demonstrated by Hahn *et al.*[71] 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."[72] 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.[73]

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.[74] Animal studies demonstrate exposure to mercury vapor and autoimmunity.[75] 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.[76]

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

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

[71] 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).

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

[73] 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).

[74] 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.

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

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

filling was associated with a 2.4 dB decline in hearing threshold (95% confidence interval [CI], 1.3-3.5 dB).[77]

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.

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.[78] [79] [80] [81] 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.

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

[78] *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.)

[79] 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.)

[80] 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.)

[81] 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.)

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. 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.)[82] 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.[83] 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.[84] [85] 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.[86]

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.[87] [88] [89] [90] [91] [92] Thus, as

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[82] 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).

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

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

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

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

[87] 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."

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.[93]

In 1984, the year of the NIDR/ADA Workshop, Fisher *et al.*,[94] 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:

> 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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[88] 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.

[89] 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.

[90] Sotres, L. S., *et al.*, *A Histologic Study of Gingival Tissue Response to Amalgam, Silicate and Resin Restorations* J. Periodo. l40: 543-546 (1969), confirmed the Trott and Sherkat findings.

[91] 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.

[92] 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.

[93] 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.

[94] 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).

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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.[95]

11. Dental Amalgam is an Implant that Must be in Class III

a. Congress's Mandate on Classification of Medical and Dental Implants

The Medical and Dental Device Amendments of 1976, 21 U.S.C. §§360c, *et seq*., require FDA to classify dental and medical devices as follows:

> (C) In the case of a device which has been referred under paragraph (1) to a panel, and which--
>
> (i) ***is intended to be implanted in the human body*** or is purported or represented to be for a use in supporting or sustaining human life, and
>
> (ii)(I) has been introduced or delivered for introduction into interstate commerce for commercial distribution before May 28, 1976, or
>
> (II) is within a type of device which was so introduced or delivered before such date and is substantially equivalent to another device within that type, such panel shall recommend to the Secretary that the device be classified in class III unless the panel determines that classification of the device in such class is not necessary to provide reasonable assurance of its safety and effectiveness. If a panel does not recommend that such a device be classified in class III, it shall in its recommendation to the Secretary for the classification of the device set forth the reasons for not recommending classification of the device in such class.

(Emphasis added.) Amalgam is an implant in the human body and, according to the statutory language, should be placed in Class III.

b. FDA Acknowledges that Dental Amalgam is an "Implant"

Until August 4, 2009, dental amalgam was not an FDA approved dental device. There is no FDA notification of approval, no 510K, and no classification of dental amalgam in the Federal Register.

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

In 1976, Congress directed FDA to evaluate all medical (including dental) devices intended for human use and to classify them according to their safety and effectiveness. [41 FR 34099, August 12, 1976] To this day, "dental amalgam" is not listed as an accepted and classified dental device, even though it has been the most widely utilized of all dental devices.

The FDA Dental Device Division classified "Dental Mercury" as a Class I device, implicitly concluding that this material is safe and effective as a dental device. [52 FR 30082-30108, August 12, 1987] However, FDA thereafter ruled that mercury is not GRAS (Generally Recognized to be Safe). [63 FR 19799-19802, April 22, 1998]

Dental amalgam, when utilized as a dental filling material and placed in living tissue in a human body, is a medical/dental device that must be classified under existing law. By definition, it must be classified as an implant and automatically placed in Class III, requiring scientific proof of safety. [43 FR 32988, July 28, 1978] The FDA defines "implant" as "a device that is placed into a surgically or naturally formed cavity of the human body. A device is regarded as an implant for the purpose of this part only if it is intended to remain implanted continuously for a period of 30 days or more, unless the commissioner determines otherwise in order to protect human health." [43 FR 32994, July 28, 1978]

In 1978, the FDA Dental Device Panel requested that dental amalgam be exempted from the FDA Rule definition for "implant." [42 FR 46035, Sept. 13, 1977] The FDA Commissioner denied that request and ruled that mercury fillings were an implant. [43 FR 32988, July 28, 1978]

c. Mercury Amalgam Must be Classified in Class III

FDA Rules state: "Although no device can be regulated adequately in Class I or Class II unless there are adequate data and information establishing its safety and effectiveness, a device for which there are such data and information may nevertheless require regulation in Class III because of the public health concerns posed by its use." [42 FR 46030, 13 Sep 1977] Public health concerns have been repeatedly voiced but ultimately ignored by FDA. The scientific community has long known that elemental mercury is a highly toxic heavy metal, and many prominent scientists have recommended the discontinuation of mercury fillings as a dental restorative material.

On February 20, 2002, FDA announced a proposed rule entitled: "Dental Devices: Classification of Encapsulated Amalgam Alloy and Dental Mercury and Reclassification of Dental Mercury; Issuance of Special Controls for Amalgam Alloy." The FDA's announced intention was to reclassify Dental Mercury into Class II and accept a "capsule" containing dental mercury on one side and amalgam alloy on the other as a "safe and effective" dental device. However, 21 U.S.C. §360c, as well as the agency's own regulation, 21 C.F.R. § 860.93, requires dental amalgam to be classified into Class III. To be classified in any other class, the Dental Device Panel must file a full statement of the reasons for such classification, including "supporting documentation and data satisfying the requirements of sec. 860.7." 21 C.F.R. § 860.93(b). This regulation provides as follows:

> (a) The classification panel will recommend classification into class III of any implant or life-supporting or life-sustaining device unless the panel determines

that such classification is not necessary to provide reasonable assurance of the safety and effectiveness of the device. If the panel recommends classification or reclassification of such a device into a class other than class III, it shall set forth in its recommendation the reasons for so doing together with references to supporting documentation and data satisfying the requirements of § 860.7, and an identification of the risks to health, if any, presented by the device.

(b) The Commissioner will classify an implant or life-supporting or life-sustaining device into class III unless the Commissioner determines that such classification is not necessary to provide reasonable assurance of the safety and effectiveness of the device. If the Commissioner proposes to classify or reclassify such a device into a class other than class III, the regulation or order effecting such classification or reclassification will be accompanied by a full statement of the reasons for so doing. A statement of the reasons for not classifying or retaining the device in class III may be in the form of concurrence with the reasons for the recommendation of the classification panel, together with supporting documentation and data satisfying the requirements of § 860.7 and an identification of the risks to health, if any, presented by the device.

In September 2006, a meeting of the Dental Products Panel and the Peripheral and Central Nervous System Drugs Advisory Committee convened to consider, *inter alia*, whether the conclusions in the FDA's position statement on amalgam (the "White Paper") should be deemed "reasonable." The Joint Panels rejected the FDA contention that the use of dental amalgam may be considered safe. Clearly, no administrative record exists on which the FDA Commissioner or the Dental Device Panel could rationally conclude that there are demonstrable and reasonable assurances that mercury fillings are safe. Amalgam capsules must therefore be classified in Class III.

12. FDA is Required by NEPA to Prepare an Environmental Impact Statement

The National Environmental Policy Act of 1969 contains a declaration policy which requires the federal government to use all practicable means to create and maintain conditions under which man and nature can exist in productive harmony. Section 102 requires federal agencies to incorporate environmental considerations in their planning and decision-making through a systematic interdisciplinary approach.

The FDA received a letter dated July 28, 2008, from Dennis J. Kucinich, Chairman Domestic Policy Subcommittee of the Oversight and Government Reform Committee, regarding the requirements imposed by the National Environmental Policy Act of 1969 (NEPA) (42 U.S.C. 4371 et seq.) requiring FDA to prepare an Environmental Impact Statement (EIS), or, at a minimum, an Environmental Assessment (EA), before the FDA promulgated any final action relating to the reclassification of mercury/silver fillings. This letter stated in part:

In the face of these clear legal requirements of NEPA-and the emerging consensus of the harms to the environment from dental mercury-the FDA has maintained in conversation with Majority Staff that the FDA is not required to undertake an EIS or EA because its specific regulatory action here-reclassification and classification of dental mercury devices-merely perpetuates the status quo amount of use of

these devices and therefore does not in itself have significant effects. ***The FDA's position, however, undermines NEPA's purposes and has been expressly rejected by the courts*.** In *Louisiana v. Lee*, the Court considered the Army Corps of Engineers' argument that its renewal of permits allowing dredging in Louisiana's Lake Pontchartrain would not trigger an environmental review under NEPA because it would merely preserve the status of quo of dredging of the Lake.39 In rejecting this argument, the Court held that "[t]he renewal of these permits will not maintain a status quo, but rather will continue a course of environmental disruption begun years ago." The Court ruled that the damage from dredging was continuing and cumulative and thus the regulatory action of renewing permits, even if it did not lead to more dredging than before, would significantly affect the environment.

Here, the FDA attempts to rely on the same argument discredited in *Lee*. **While the proposed classification and reclassification of mercury-related dental devices may arguably maintain some sort of regulatory status quo, it would certainly not maintain an environmental status quo.** The continued introduction of mercury into the environment attributable to dental devices would, by dint of its highly toxic, persistent, and bioaccumulating nature, "continue a course of environmental disruption begun years ago." The load of mercury from dental devices in the air, water, and in the food chain can be expected to increase.

Recent case law has reaffirmed that before an agency eschews an EA or EIS required by NEPA, it must take a "hard look" at the environmental consequences of a proposed action, including a consideration of all foreseeable direct and indirect action. After undertaking such a "hard look," an agency must put forth a "convincing statement" of reasons that explain why the agency action will impact the environment no more than insignifrcantly. Without such an analysis, courts have reversed agency determination as "arbitrary and capricious" pursuant to the Administrative Procedure Act. Here, the FDA's position seems to have been manufactured primarily for the purpose of stymieing this Subcommittee's inquiry. In response to the Subcommittee document request, it was notable how little consideration the FDA has ever given NEPA requirements when classifying mercury-related dental mercury. **The documents produced to the Subcommittee added little to the FDA's cursory unexamined invocations of its own categorical exclusions found in its rulemaking.** The FDA certainly provided no contemporaneous documentation demonstrating its consideration of the environmental consequences of its rulemaking in 1980, 1987, or 2002; no analysis whether its proposed action met the specific criteria of this categorical exclusion in 1987; no evidence that it was relying on the "status quo" legal theory at any time from 1980 onward; and no acknowledgement more recently that the EPA, states, and localities were scrambling to implement controls on dental mercury in response to the growing body of scientific knowledge that demonstrated the scope and scale of specific harms caused by the introduction of dental mercury into the environment. **Instead, it appears that the FDA's position is a post hoc rationalizafion of the FDA's decision to ignore NEPA's mandates.** [Emphasis added.]

The FDA claims that NEPA does not apply because FDA is entitled to a categorical exclusion. As Congressman Kucinich says, "FDA's cursory unexamined invocations of its own categorical exclusions found in its rulemaking. In reality the CFR places a different requirement on the FDA:

40 C.F.R. § 1508.4 **Categorical Exclusion.**

> Categorical Exclusion means **a category of actions which do not individually or cumulatively have a significant effect on the human environment** and which have been found to have no such effect in procedures adopted by a Federal agency in implementation of these regulations (§ 1507.3) and for which, therefore, neither an environmental assessment nor an environmental impact statement is required. An agency may decide in its procedures or otherwise, to prepare environmental assessments for the reasons stated in § 1508.9 even though it is not required to do so. Any procedures under this section shall provide for extraordinary circumstances in which a normally excluded action may have a significant environmental effect. (Emphasis added)

A "Categorical Exclusion" does not apply to the classification of dental amalgam. In reality the FDA should have done an EIS soon after the act was passed in 1976 and certainly by the time mercury was put in Class I in 1987. The FDA's failure to do an EIS in 2009 is indefensible.

In its Final Rule, FDA refers to comments stating that an Environmental Impact Statement ("EIS") was required and ignored by FDA replied: "These comments reflect a misunderstanding of the action FDA is taking in this final rule and it obligations under NEPA for such action. The comments presume that FDA has a general obligation under NEPA, in the context of promulgating this final rule, to assess the impacts of mercury on the environment and the effects of any continued introduction of mercury attributable to dental devices. FDA disagrees with such a presumption, particularly where there is 'no reasonably close causal relationship' between the actions in the final rule and such general impacts." (*Citing*, *Department of Transp. v. Public Citizen*, 541 U.S. 752, 767, (2004).) However, the cited case does not support FDA's position. Unlike the FDA, the agency in the DOT case had no control over the alleged environmental contamination at issue. The Court held that because FMCSA lacked discretion to prevent cross-border operations of Mexican motor carriers, neither NEPA nor the Clean Air Act required FMCSA to evaluate environmental effects of such operations. FMCSA had no statutory authority to impose or enforce emissions controls or to establish environmental requirements unrelated to motor carrier safety. Motor Carriers Safety Improvement Act of 1999, § 101(a), 113 Stat. 1750; 49 U.S.C.A. § 13902(a)(1).

In the case of dental amalgam, FDA may ban the product, require that separators be used in dental offices, warn about improper discharge of the product, or limit the use of mercury fillings thus alleviating the environmental impact. FDA's reliance on the DOT case is misplaced.

All, or virtually all, of the references cited herein were submitted with the Citizen's Petition filed by the International Academy of Oral Medicine and Toxicology (and other Petitioners) and dated July 25, 2009.

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