ADDENDUM TO THE WHITE PAPER

Addendum to the Dental Amalgam White Paper: Response to 2006 Joint Advisory Panel Comments and Recommendations

Center for Devices and Radiological Health
U.S Food and Drug Administration
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This Addendum was prepared in response to the recommendations of the Dental Products Panel and the Peripheral and Central Nervous System Drugs Advisory Committee (the Panel) concerning a 2006 White Paper presented in draft form to the Panel on September 6 and 7, 2006. FDA prepared this Addendum to address the Panel's comments on the White Paper.

The 2006 draft White Paper and 2009 Addendum constitute FDA's final White Paper.

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I. Executive Summary

The combined CDRH Dental Products Advisory Committee and the CDER Peripheral and Central Nervous System Drugs Advisory Committee met September 6-7, 2006. The joint committee (the Panel) reviewed and discussed the FDA's *Draft – Update/Review of Potential Adverse Health Risks Associated with Exposure to Mercury in Dental Amalgam*, a summary of the most recent and relevant peer-reviewed scientific literature on exposure to dental amalgam mercury and potential adverse responses. The primary focus of the White Paper (2006) was to address potential neurotoxic effects of dental amalgam mercury, the most frequent concern raised by consumer inquiries and letters to the Agency. Recent U.S. government agency reviews of mercury toxicity published in 1999 (ATSDR), 2003 (EPA), and 2005 (ATSDR) were used to support the review for studies published from 1997-2002. In order to evaluate the peer-reviewed scientific literature published subsequent to these major reviews, a PubMed search for the years 2003-2006 identified additional relevant articles, and articles that met a set of inclusion criteria (White Paper, Appendix A, 2006) were considered for the review. A series of primary research articles (reviews and letters to the editor were not considered) were chosen for their scientific merit and relevance (human exposures to dental amalgam and/or elemental mercury vapor; animal studies of maternal exposure and outcomes in offspring), and potential to provide the most significant and new information regarding the health risks associated with exposure to mercury vapor.

In general, the Panel agreed with FDA's conclusion that there was no direct evidence showing adverse health effects from dental amalgam in the general population. The Panel also expressed concerns about certain aspects of FDA's methodology (primarily that the PubMed database was the only database queried) in identifying the studies that FDA considered the most relevant and reviewed for the White Paper, as well as gaps in the available scientific data on the effects of dental amalgam on specific populations with potentially greater sensitivity to mercury.

During their deliberations, a general consensus was reached among Panel members that the recently published prospective human clinical trials (Bellinger et al., 2006; DeRouen et al., 2006) evaluated in the White Paper were well-designed and gave direct evidence of the safety of amalgam when comparing neuropsychological outcomes between children receiving amalgam vs. children receiving composite restorations. Panel members also acknowledged that the present state of knowledge on chronic health effects was well covered in the White Paper.

In response to the deliberations and recommendations from the Panel, FDA conducted a more in-depth review of the scientific literature. A description of the Panel recommendations and the process of identifying relevant studies to address the recommendations are discussed in this Addendum.

A. Conclusions of the White Paper and Addendum

The articles and studies reviewed for the Addendum to the White Paper also support the conclusions in the original FDA White Paper and those of a preponderance of other U.S. government and international organization reviews on the safety of dental amalgam. The following conclusions are a result of the FDA review of over 200 scientific articles (primarily peer-reviewed scientific research articles and case studies) considered in the White Paper and Addendum to the White Paper.

1. Elemental mercury vapor is released from dental amalgam, and higher amounts are released with mastication and gum chewing. Mercury from amalgam is absorbed (80% of the dose primarily via the lungs), is systemically distributed, and excretion occurs generally via the urinary route.

2. Elemental mercury vapor has a well-studied toxicity profile and its toxicity is dependent on dose and exposure conditions. Individuals with amalgam restorations generally have urinary mercury concentrations that are higher than individuals with no amalgams; however, these concentrations are lower than those concentrations associated with adverse outcomes resulting from high occupational exposures to mercury vapor. Scientific studies have estimated that dental amalgam exposes adults to amounts of mercury vapor below or approximately equivalent to health-based exposure reference levels established to protect the health of all populations.

3. The benefits of dental amalgam as a dental restorative material generally outweigh the risks of adverse health effects in the population age six and older. Studies have provided evidence showing no association between exposures to mercury vapor, either occupationally or from dental amalgam, and Alzheimer's disease. Other studies have provided evidence showing no association between neurological and neurobehavioral (motor and cognitive) effects or renal damage. There is a paucity of studies that evaluate a link between dental amalgam mercury vapor exposure and other neurodegenerative diseases such as Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, and autism.

4. Some patients appear to exhibit exacerbated allergic reactions and develop mucosal conditions (e.g., oral lichen planus) as a result of exposure to dental amalgam. When dental amalgams are removed from patients with mercury allergy or other immune-related responses, the conditions often resolve.

5. Studies to date have not revealed any increased risks of adverse effects on reproductive health in women from exposure to dental amalgam. Limited or, in some cases, no information is available regarding long-term adverse health outcomes in specific populations, such as pregnant women or their offspring as a result of prenatal or postnatal (breast milk) exposures to dental amalgam mercury, in children less than six years old, or in persons with neurological or renal dysfunction. Recent prospective clinical studies, however, have failed to demonstrate neurological or renal deficits in children who first received dental amalgam restorations at age six.

6. Dental professionals who prepare and place dental amalgam restorations are exposed to mercury in the workplace and generally have higher urinary mercury concentrations than patients; however, the weight of evidence from many studies, when considered together, does not suggest adverse effects resulting from exposures in these cohorts. Nonetheless, since exposures in the workplace can be higher in dental professional compared to their patients, this population should be studied further. All dental clinics should adhere to practices which mitigate mercury vapor exposures.

7. The analysis of 33 case studies, defined as reports consisting of information from one to approximately 10 individuals that generally do not include control subjects, generally confirmed conclusions of earlier dental amalgam reviews, and offered no new insights or concerns. Various dermatological conditions or lesions of the skin, mouth and tongue were attributed to either direct or indirect contact with dental amalgam, and may be related, at least in part, to a pre-existing hypersensitivity or allergy to mercury (and usually other metals). In cases where amalgam restorations were removed, there was a resolution of signs and symptoms. In most cases, conclusions from case studies reviewed are difficult to draw beyond the particular case, as there are no control subjects.

II. Recommendations of the Joint Advisory Panel for Improving the White Paper Methodology and Content and FDA Responses to the Recommendations

The following list represents major and minor recommendations that were defined during the Panel deliberations and is followed by a brief response on how each recommendation was addressed by FDA.

- The Panel sought more detailed information on the selection and ranking criteria for the studies chosen for the FDA review and the remaining studies not chosen for in-depth review. Specifically, the Panel members suggested that the FDA review was limited to a single database and recommended searches of additional literature databases, which might yield additional relevant studies. However, the Panel noted that even with additional literature database searches and the review of additional papers, the White Paper conclusions may not change.

    - FDA Response: This concern was addressed by using two additional databases for primary research studies. In addition, studies submitted to FDA during the public comment period after the 2006 Advisory Panel meeting were considered and reviewed when appropriate. This effort comprised a major portion of the Addendum to the 2006 White Paper and details of this review process are highlighted in the Addendum section.

- In addition to the expanded review for primary research studies, the Panel also recommended literature searches to identify and review relevant reports of case studies, which might reveal adverse health signals that would lead to development of hypotheses for additional controlled studies or illuminate health risks.

    - Case studies were reviewed as a result of a specific search of three literature databases. This effort comprised a major portion of the Addendum to the 2006White Paper and details of this review process are highlighted in the Addendum section.

- Another major recommendation from the Panel was that FDA consider a closer evaluation of studies, if available, providing information about risks to specific populations, such as pregnant women, developing fetuses, children, and persons with allergies or autoimmune diseases, who may be more vulnerable to mercury. The Panel expressed the view that apparent gaps in the literature reviewed in the White Paper may simply reflect gaps in the available research.

    - Recent studies in these areas of concern were reviewed in the White Paper and Addendum, and Data Gaps are addressed in the Addendum.

- Identify research or gaps in research examining issues of allergy and autoimmune function related to mercury exposure.

    - Recent studies in this area are reviewed in the Addendum.

- Identify research or gaps in research which address the concentrations of mercury vapor after acute short term exposure (i.e., at time of amalgam placement).

    - Given the chronic nature of exposure to mercury vapor with dental amalgam restorations, the short-term, albeit higher, levels of mercury vapor generated during amalgam placement are unlikely to impact the long-term effects of exposure to levels generated from amalgam fillings. The validity of analytical techniques used to measure intraoral mercury remains controversial, as was evident in the proceedings of the 2006 Advisory Panels meeting. Further, the scientific validity of comparing intraoral mercury vapor concentrations to government health-based reference values, such as the ATSDR MRL, is questionable.

- Compare exposure values from amalgam to those for chronic mercury exposure values (e.g., occupational, non-amalgam-related exposures).

    - Occupational exposure levels and exposure levels associated with dental amalgam were both reviewed and compared in the White Paper and Addendum. In general, occupational exposures are generally much higher than those noted for exposure to dental amalgam and therefore, often do not provide data directly relevant to dental amalgam exposures.

- Present a pharmacokinetic description or model of absorption, distribution, and excretion of mercury vapor from dental amalgam.

    - The pharmacokinetic behavior of major forms of mercury has been well-studied and reported [for a recent review, see T Clarkson and L Magos, *The toxicology of mercury and its chemical compounds* (Critical Reviews in Toxicology 36:609-662, 2006)]. As described in the White Paper and many other sources, it is well-documented that mercury vapor from amalgams is absorbed by the body and is systemically distributed, including to the brain and fetus. The issue is whether or not the tissue concentrations observed after amalgam placement present appreciable risk of adverse outcome. Further development of pharmacokinetic data and/or models, unless expected to show that mercury does not reach potential susceptible tissues, would not further the process of determining risk. Thus, this recommendation was not pursued.

- Conduct a safety review of alternative, non-amalgam restorative materials.

- A review of the safety of alternative materials was beyond the focus of the current review, i.e., dental amalgam. A review of the potential risks associated with alternative restorative materials can be found in the European Commission – Scientific Committee on Emerging and Newly Identified Health Risks Preliminary *Report - The safety of dental amalgam and alternative dental restoration materials for patients and users* (released November 2007).

- Evaluate autopsy studies of mercury concentrations in brain.

    - Four studies reporting on mercury concentrations in autopsy tissue were reviewed in the Addendum. In general, autopsy studies provide very limited information with respect to evaluating health risks of exposure to dental amalgam. Drawing meaningful conclusions between neurodegenerative disorders, the number of dental amalgams, and the amount of accumulated mercury in the brain is difficult, in part because it is possible that damaged neuronal cells in patients with neurodegenerative disorders accumulate more mercury than healthy cells, and in part due to the unknown histories of fish consumption or other environmental or occupational mercury exposures in these study cohorts.

- Evaluate studies of other sources of mercury exposure, e.g., environmental (air, water contamination), and the cumulative effect of eating fish, that would increase the total exposure to mercury.

    - This type of comprehensive analysis of exposure to multiple species of mercury from multiple sources was beyond the scope of the review. One study that was reviewed demonstrated that hair mercury concentrations were associated with fish consumption and not number of dental amalgam fillings, whereas urinary mercury concentrations were more relevant to number of mercury amalgams.

- Identify issues of biological variability (e.g., persons who excrete mercury poorly or who accumulate higher body burdens).

    - These issues were covered in part in the present Addendum. One study showed gender differences in mercury excretion after dental amalgam placement and indicated mercury excretion in females is higher than males and suggested the possibility that males might be more susceptible to adverse reactions to mercury.

- Evaluate studies which address the clinical relevance of mercury concentrations in urine, blood and hair as indicators of exposure.

    - Urinary concentrations and rate of excretion of mercury are the most frequently used and are widely accepted as the gold standard biomarkers of exposure to mercury vapor. Inorganic mercury, including mercury vapor, is accumulated in

hair only to a very small extent, if at all. Scalp hair and blood are the most appropriate biomarkers of exposure to organic forms of mercury, such as methylmercury from seafood. Recent data suggest that hair mercury concentrations are not impacted by number of dental amalgam fillings in children.

- Evaluate the environmental impact of amalgam waste from dental offices.
    - This recommendation is beyond the scope of the current review. Standards (e.g., from the American National Standards Institute) are available for environmentally responsible amalgam waste management in dental offices.

- Re-consider interpretation of the control subjects used in some of the Echeverria et al. dental personnel studies.
    - This was a valid scientific criticism. The criticism of the relevant Echeverria studies should have indicated that "no non-mercury exposed dental professionals" were included as controls. In the White Paper it was stated that a weakness of some of the Echeverria studies was that there were ''no non-dental professional controls."

The Panel offered other recommendations and observations. Several members of the Panel suggested that the FDA apply the precautionary principle as currently practiced by other countries to the use of dental amalgam to protect some populations which might be more vulnerable to the effects of mercury exposure, such as young children. The Panel wanted patients to have accurate information about the composition of dental amalgams. Several Panel members suggested there be a requirement for informed consent.

- FDA agrees that the relative risks and benefits of all dental materials be discussed by dentists with their patients.

III. Approach to the Review of Additional Scientific Literature for the White Paper Addendum

A major concern addressed by the Joint Advisory Panel related to the potential inadequacy of searching only one literature database (PubMed), which might have missed some critical studies. Therefore, a major effort for this Addendum involved a search of three major literature databases that were conducted to complement the original search for the FDA 2006 White Paper; all new searches described below included search terms provided in Appendix B of that document. Additional standard search strategies were employed to eliminate duplicate citations obtained in the original 2006 literature database searches. Other terms were employed to search specifically for case reports and case studies (see section 2 below). Articles selected for in-depth review were primary research articles or case reports/studies as well as scientific citations submitted to the Agency docket via public comment after the September 2006 Advisory Panel joint meeting. The bibliography for the References reviewed for this Addendum is provided at the end of the document. For each citation, a code is provided to identify from which of the three databases the article originated, and a code and rationale for why a particular reference was not reviewed.

1. **Additional search databases.** The Panel recommended that additional search engines might have yielded additional papers to be included in the review.

For the 2006 White Paper, a search of PubMed covering 2003-May 2006 identified 202 relevant articles. This bibliography, including the abstracts, was reviewed for articles that met scientific-based inclusion criteria (2006 White Paper, Appendix A) in order to select articles for in-depth review. From this screening, 24 peer-reviewed articles were chosen for their scientific merit, luminosity, and relevance (human exposures to dental amalgam and elemental mercury vapor; animal studies employing mercury vapor exposures), and potential to provide the most significant and new information regarding the health risks associated with exposure to mercury vapor. An additional 12 articles used in several recent U.S. government agency reviews were included in the White Paper review because of their high relevance. Thus, the majority of the White Paper focused on the in-depth evaluation of 34 peer-reviewed, primary research articles. Major U.S. Public Health Service agency reviews (ATSDR, 1999, 2005; EPA – 2002) on mercury health effects were also used to support the White Paper assessment of health risks from mercury in dental amalgam.

For this Addendum, literature searches using two additional databases were conducted. Using the search criteria established in the White Paper in 2006, the EMBASE and Biosis databases were searched for the years 2003-2008. A fourth database, Toxline, was searched but found no unique articles. In addition, a “catch-up” search for PubMed was conducted for the period May 2006-2008 for articles published since the 2006 White Paper search. Searches were designed to eliminate any duplicates from the previous searches in order to exclude citations previously considered for the 2006 White Paper.

In these most recent searches, 38 new citations were identified that were not identified in the original White Paper literature searches. Of the 38 citations, 12 references were not reviewed based on review inclusion criteria (see 2006 White Paper, Appendix A; and the reference list for this Addendum). The omitted references consisted primarily of letters to the editor, editorials, and review articles.

2. **Case studies and reports.** The Panel recommended that an evaluation of case studies and reports be included in a White Paper Addendum.

It was suggested by the Panel that case studies and reports – which generally consist of sometimes a single subject or less than 10 subjects and no control subjects, and by nature lack scientific robustness – might reveal biological signals and/or hypotheses for further consideration. The databases searched for case studies and reports were PubMed, EMBASE, and Biosis covering 1996-2008.

In the literature database searches for case studies and reports, 64 total citations were identified, including 27 epidemiology studies, characterized by larger cohorts, control groups, and greater robustness. Of the 64 citations, 5 were deemed inappropriate or did not meet the FDA review inclusion criteria (see 2006 White Paper, Appendix A; and the reference list for this Addendum).

3. **Citations from public comments.** Immediately following the September 2006 Panel Meeting, the Agency opened a docket to allow for additional comments from the public. Publications from 1996-2007 were sometimes included in these comments and were reviewed as part of the Addendum when appropriate. The docket closed on November 9, 2006, and out of 2400+ comments, 90 citations were identified. The 90 citations consisted of a variety of document types (e.g., peer-reviewed primary research articles, books, review articles, a Powerpoint presentation, US and international government reports, non-English articles, and articles previously reviewed in the 2006 FDA White Paper). Of the 90 citations, 24 did not meet the review inclusion criteria (see 2006 White Paper, Appendix A; and the reference list for this Addendum) or were previously reviewed in the original 2006 White Paper. Five of these publications were also identified in the Case Reports/Studies literature search. Four very recent articles were also reviewed after public presentation to the FDA and were considered as part of the Public Comment database.

The studies reviewed from the literature database searches and the public comments were placed into the following categories (number of studies reviewed):

Human studies

- Developmental/reproductive system (8)
- Nervous system (14)
- Immune system (8)
- Occupational exposure (12)

- Pharmacokinetics/body burden (20)
- Susceptible/sensitive populations (5)
- Cardiovascular system (1)
- Cancer (3)

Animal studies

- Developmental disposition and toxicity (5)
- Immune system/susceptible populations (3)
- Nervous system (3)
- Antibiotic resistance (3)

Case studies

- Skin and mucous membranes (15)
- Nervous system (5)
- Pulmonary system (3)
- Gastrointestinal system (1)
- Musculoskeletal system (1)
- Mercury poisoning (acrodynia) (5)
- Chelation (3)

IV. Review of Peer-reviewed Articles Related to Dental Amalgam Mercury

(unless otherwise specified, the terms 'Hg' and 'mercury' refer to total mercury measured and include both organic and inorganic forms)

Human Developmental/Reproductive Systems (8)

Bjornberg et al. (2005) reported in a study of Swedish mothers that fetal/infant exposure to both methylmercury and inorganic mercury is higher before birth than during breastfeeding and that methylmercury contributes more than inorganic mercury to infant total mercury exposure postnatally via breast milk. Maternal blood inorganic mercury concentrations correlated significantly with number of amalgam-filled surfaces at birth. Concentrations of both methylmercury and inorganic mercury in infant (cord) blood at birth were highly associated with maternal blood concentrations of both at birth and both decreased significantly out to 13 weeks of age. Concentrations of both mercury species were low at all time points: median maternal and infant blood concentrations of methylmercury were all less than 1.2 µg/L, and concentrations of inorganic mercury were all less than 0.1 µg/L. Total mercury in breast milk correlated with infant blood concentrations of methylmercury but not inorganic mercury.

da Costa et al. (2005) demonstrated that the amount of mercury in breast milk during the first month post-partum correlates with the number of maternal amalgam surfaces and that in some infants, exposure to mercury via breast milk will be above 0.5 µg/kg body weight.

Gerhard et al. (1998) reported in an observational study examining the potential associations of heavy metals with fertility that concentrations of mercury in saliva increase with number of amalgams and that chewing increases these concentrations. In addition, chelation with DMPS greatly increased urinary concentrations (excretion) of mercury. The authors also noted an increase in the frequency of luteal insufficiency in women with high urinary mercury excretion, but it was not clear if that finding was statistically significant. The authors concluded that their results could not permit causative analytical conclusions.

Gerhard & Wallis (2002) present pilot data from studies conducted to establish whether pathological sperm parameters can be improved through individualized-homeopathic therapy. Variables from patients' histories were studied in detail for their influence on patient response to homeopathy and associations between sperm count changes and hormone concentrations were evaluated. The authors observed that patients with a higher number of amalgam fillings (>5) exhibited much less improvement under homeopathic therapy than patients with fewer amalgam fillings. The authors note that animal studies and measurements in workers exposed to organic mercury compounds in pesticide production plants confirm that nontoxic concentrations of mercury in the air or diet induce reduction in sperm motility and fertility.

Lutz et al. (1996) determined mercury, cadmium, and lead concentrations in autopsy specimens of brain and kidney of second trimester fetuses aborted prior to partuition and infants less than 3 months of age. Renal concentrations of mercury (6 µg/kg in fetuses; 10 µg/kg in infants) were

significantly higher than in brain (4 µg/kg in both fetuses and infants). There was a tendency of increasing mercury concentrations in fetal kidney, but not brain, with increasing number of maternal amalgams**.** These findings should be interpreted with caution due to the small number of subjects and high variation in the number of amalgams/kidney mercury concentration ratios.

Oskarsson et al. (1996) looked at total and inorganic mercury in breast milk and blood in relation to fish consumption and amalgam fillings and found that exposure of the infant to mercury from breast milk was calculated to range up to 0.3 µg/kg/day, of which approximately one-half was inorganic mercury, the source of which was maternal amalgam. These exposures correspond to approximately one-half the tolerable daily intake recommended by WHO for adults.

Ursinyova and Masanova (2005) also looked at mercury concentrations in breast milk in 158 Slovakian women and found the average mercury concentration to be 0.94 µg/kg [~0.94 µg/L]. The average calculated dietary intake of mercury in newborns was far below the provisionally tolerable weekly intakes (PTWIs) established by WHO. A positive correlation between number of maternal teeth fillings and mercury concentration in breast milk was reported.

Vimy et al. (1997) reported data from animal studies (sheep) showing that during pregnancy, a primary fetal site of mercury concentration from maternal amalgam is the liver, and, after birth, the kidney. In the same report, an analysis of lactating women with aged amalgam fillings showed that mercury excretion in breast milk and urine correlated with number of fillings. Comparing mercury concentrations in breast milk from women with dental amalgams with those without amalgams, the mercury concentration in breast milk attributed exclusively to amalgams is ~ 0.09 µg/L. A daily milk intake of 0.85 L would translate these results into an infant exposure via dental amalgam of 75 ng/day (0.075 µg/day). Given that dental amalgam placement or removal greatly, but temporarily, increases mercury exposure from the amalgam, the authors recommended avoiding these procedures in pregnant or lactating women.

Summary of reports related to human developmental/reproductive systems

The data in this section add to the larger literature showing that mercury concentrations in saliva, urine, breast milk, and blood, and other tissue concentrations (e.g., kidney but not brain) correlate with number of dental amalgams. The data also confirm that exposure of fetuses to both methylmercury and inorganic mercury are very low, with exposures decreasing after birth while breastfeeding. The average dietary intake of mercury in newborns is well below the provisional tolerable weekly intakes (PTWIs) established by WHO. No health effects were monitored in most studies: reports of luteal insufficiency or effects on sperm count did not demonstrate convincing effects. Based on the study Vimy et al. (1997), the daily exposure to inorganic mercury from breastfeeding for a 5-kg infant would be 0.015 µg Hg/kg/day. The EPA has set a Reference Dose (RfD)[1] for oral exposure to inorganic mercury at 0.3 µg Hg/kg/day. Thus, the estimated concentration of mercury in breast milk attributable to dental amalgam

exposure is low and is an order of magnitude below the health-based exposure reference value for oral exposure to inorganic mercury established to protect the health of adults and children.

Human Nervous System (14)

Bailer et al. (2001) compared 40 women who were convinced their complaints were caused by exposure to mercury in amalgam fillings ("amalgam sensitive subjects"; urinary mercury concentrations of 2.33 μg/g creatinine) with 43 women who did not hold this belief ("amalgam nonsensitive controls"; urinary mercury concentrations of 2.24 μg/g creatinine) with respect to various dental, medical, toxicological, and psychological variables. The authors report the amalgam-sensitive women had a higher prevalence of medically unexplained somatic symptoms than the control subjects and suggest that self-diagnosed amalgam illness is a label for general tendency toward somatization. Unexpectedly, higher mercury concentrations in the saliva of the subjects correlated with lower physical symptoms on the somatization scale. The authors noted that the findings from only moderately impaired nonclinical amalgam sensitive subjects may not generalize to patients with more severe amalgam illness; and the study does not allow separating the extent to which the psychological abnormalities of the amalgam sensitive patients were either the cause or consequence of somatic complaints.

Cornett et al. (1998) analyzed brain concentrations of 4 elements (iron, zinc, mercury and selenium) in the brains of 58 Alzheimer's disease (AD) patients and 21 controls obtained at autopsy. These metals had been previously implicated in free-radical induced oxidative stress in AD. While there was a statistically significant increase in iron and zinc in several regions within AD brains, there was no significant difference in mercury concentrations. A significant increase in selenium was noted in only the amygdala of AD patients. The authors conclude that elevations of zinc and iron in the AD brain have the potential to augment neuron degeneration.

Gottwald et al. (2002) compared 40 patients with amalgam-related complaints with a well-matched group of 40 patients without complaints. Blood and urinary mercury concentrations did not differ between the groups. The authors found no indication for mercury intoxication or amalgam allergy as a cause of the patients' complaints and conclude that amalgam-related complaints are an expression of underlying psychic problems and believe treatment should focus on somatization and assisting patients with coping strategies. The authors recognize their study design cannot rule out whether amalgam patients react more sensitively to the body sensations or are more sensitive to the smallest amounts of mercury that are well tolerated by others.

Grandjean et al. (1997) present a study indicating patients with environmental illness may benefit from placebo. The subjects included 15 men and 35 women, all with at least four amalgam fillings and all with amalgam-attributed symptoms lasting at least 6 months. The study was designed as a double-blind, randomized, placebo-controlled trial. Patients who attributed their symptoms to dental amalgam fillings showed increased distress, in particular in

the somatization, obsessive-compulsive, depression, and anxiety dimensions. Chelation treatment was effective in augmenting urinary excretion of both mercury and lead. As a result of the therapy, the patients expressed overall improvement in their condition, but there was no difference between patients who had received an active chelator and those who had not. The authors suggest further exploration of the possibility that certain patients with environmental illness are particularly likely to exhibit a substantial placebo effect.

Hock et al. (1998) measured blood mercury concentrations in Alzheimer's disease (AD) patients (n=33) and compared them to age-matched control patients with major depression (MD) (n=45) and to an additional control group of patients with various non-psychiatric disorders (n=65). Blood mercury concentrations were more than two-fold higher in the AD group compared to control patients with MD (2.64 ± 0.38 μg/L vs. 1.20 ± 0.20, respectively). Blood mercury concentrations in AD patients with early onset of the disease were almost three-fold higher (3.32 ± 0.73 μg/L, n=13). Blood mercury concentrations in AD patients with late onset disease were also significantly higher (2.20 ± 0.39 μg/L) compared to the controls. Patients with non-psychiatric disorders had an average blood mercury concentration of 1.09 ± 0.12 μg/L. These correlations provide no evidence of causality related to mercury amalgam for the pathogenesis of AD; the higher mercury concentrations were unrelated to dental status. At the time of this study, the average blood mercury concentrations in Germany were 0.74 ± 0.8 μg/L. [Mean total mercury concentrations in blood in the general population reported in the 1999 ATSDR Toxicological Profile for Mercury were 1-8 μg/L; the arithmetic and geometric mean blood concentrations for dentate women in the U.S. was 2.02 and 1.04 μg/L, respectively (Dye et al., 2005)]. The study was not designed to determine whether or not elevated blood mercury concentrations in AD patients is due to mercury sequestered in brain being released with resultant neuronal death due to AD. Another finding of the study was the correlation of blood mercury concentrations with CSF concentrations of amyloid β-peptide, but not tau protein. The number of amalgams was assessed. No correlations between amalgam status and blood mercury concentrations between AD and MD patients was observed. Blood mercury is comprised of the sum of organic (methylmercury) and inorganic (elemental mercury, inorganic salts) mercury from a variety of sources. Because of the retrospective study design, the unknown sources of mercury detected in blood, and the lack of correlation of blood mercury concentrations with dental amalgam status, it is not possible to establish a relationship between AD and dental amalgam.

Holmes et al. (2003) examined the concentrations of mercury in first baby haircuts. Hair samples (collected between 1 and 2 years of age) were analyzed when the children were 2 to 15 years old, suggesting that the age of the samples ranged from 0 to 13 years. The authors reported that hair mercury concentrations of autistic children were significantly lower than those of non-autistic children. The authors suggested the possibility that autistic children do not excrete mercury as well as non-autistic children and, thus, less mercury is deposited in hair. Concentrations of mercury in the hair of non-autistic children increased with number of maternal amalgams, whereas they did not in autistic children. No mercury hair concentrations of the siblings of autistic children were presented. The authors recognized that their study was not prospective, that recruitment of subjects was influenced by medical-care seeking behavior,

and that the population of autistics tested may not represent the autism population as a whole. They further suggest that additional research is necessary to replicate their findings and to explore the major risk factors associated with mercury exposure.

Huggins and Levy (1998) report on four persons with multiple sclerosis (MS) and protein changes in the cerebrospinal fluid (CSF) after: amalgam removal and replacement with composite fillings, removal of root canal filled teeth and other infected teeth, treatment with Vitamin C, and several detoxification procedures. In addition, treatment included medical, dental, psychological, nursing, nutritional, and neuromuscular therapies. While there were clear changes in the CSF protein profiles after treatment, there were no non-MS controls and the plethora of manipulations that accompanied amalgam removal makes the relevance of the findings to dental amalgam mercury exposure unknown.

Kidd (2000) surveyed 60 patients who had dental amalgam replacement accompanied by a protocol of nutritional support, antioxidant therapy and heavy metal detoxification using the chelator dimercapto-propane-sulphonate (DMPS) and neural therapy. The survey studied only the patients' estimations of their most distressing symptoms and their evaluations of response to treatment. The most common complaints were problems with memory and/or concentration; muscle and/or joint pain; anxiety and insomnia; stomach, bowel, and bladder complaints; depression; food or chemical sensitivities; numbness or tingling; and eye symptoms, in descending order of frequency. Headache and backache responded best to treatment, but all symptoms showed considerable improvement on average. Of the respondents, 78% reported they were either satisfied or very satisfied with the results of treatment, and 9.5% reported they were disappointed. The author opines that, while the characteristic symptoms of mercury poisoning have been known for almost 200 years, a wide range of symptoms from migraine to cardiac palpitations to bladder and bowel disturbance is possible because the autonomic system may also be involved. The lack of control subjects and the multiple therapeutic interventions that accompanied amalgam removal make it impossible to know if amalgam removal alone would have resulted in similar observations.

Lindh et al. (2002) evaluated the effects of removing dental metals and providing concomitant antioxidant therapy for patients suffering from ill health with a multitude of symptoms (the dominant initial symptom was chronic fatigue) associated with metal exposure from dental amalgam and other metal alloys. The treatment was implemented according to the 'Uppsala model' based on close cooperation between physicians and dentists. Patients (n=796) in a retrospective study responded via questionnaire about symptom changes, changes in quality of life as a consequence of treatment, and assessment of caretaking. More than 70% of the responders reported substantial recovery and increased quality of life after the removal of amalgam and treatment and concomitant antioxidant therapy. Plasma concentrations of mercury were lower after amalgam removal, prompting the authors to posit that the metal exposure was the causative factor for the ill health. The authors provide hypotheses which they believe may help to account for the clinical effects noted and point out that decreased amounts of selenium are associated with mercury exposure. Given the retrospective nature of

the study, the lack of controls and other concomitant treatments, it is not possible to determine the effect of removal of dental amalgam alone.

Ng et al. (2007) conducted a meta-analysis of the literature from 1980 to 2003 (search string 'mercury'). The authors reported that while hair mercury concentrations correlated with mercury concentrations in blood, 24 hour urine, and cord blood, they should not be used instead of blood or urinary concentrations in clinical decision making for individuals. They report that the epidemiological evidence shows that low-level mercury exposure is not a cause of autism (relative risk = 0.49).

Siblerud et al. (1998) describe a pilot study that compared before and after treatment scores on the Minnesota Multiphasic Personality Inventory-2 (MMPI-2) for 11 manic depression patients who had their amalgam fillings removed and for 9 subjects with amalgams who were told they were being given a placebo or sealant. The amalgam removal group improved significantly in 47 of the 87 scales evaluated. Depression and hypomania scores improved significantly, as did anxiety, anger, schizophrenia, paranoia, and many others. The amalgam removal group reported a 42% decrease in the number of somatic health problems after amalgam removal, compared to an 8% increase in somatic symptoms in the placebo/sealant group when comparing a before-and-after health questionnaire. The authors refer to the theory that depression from amalgam mercury may result because mercury has the ability to affect certain neurotransmitters whose disruption causes manic depression (bipolar disorder). They recommend further studies with larger numbers to validate the initial findings and to help elucidate amalgam mercury's role as an etiological factor in depression. Given the small number of subjects and the absence of any measures of mercury in blood or urine, it is not possible to conclude that decreasing mercury exposure via removal of dental amalgam is related to changes in clinical observations.

Sibelrud et al. (1999) describe another pilot study that compared scores on the MMPI-2, the Millon Clinical Multiaxial Inventory-II (MCMI-II), and the Symptom Check List-90 (SCL-90) before dental amalgam removal in eight schizophrenic patients to scores in the same subjects 6 months after amalgam removal. Significant improvement was found in 41 of the 61 component scales of the MMPI-2 and 12 of the 20 subscales including schizophrenia, hysteria, paranoia, and anger. Sixteen of the 25 diagnostic scales improved significantly in the MCMI-II including schizoid, anxiety disorders, thought disorders, and bipolar symptoms. Four of nine dimensions improved significantly in the SCL-90 including depression, psychoticism, and obsessive-compulsive. The authors hypothesize that removal of the mercury dental fillings may have contributed to the improved mental health. Given the small number of subjects and the absence of any measures of mercury in blood or urine, it is not possible to conclude that decreasing mercury exposure via removal of dental amalgam is related to changes in clinical observations.

Wojcik et al. (2006) evaluated a population of several hundred patients from a general medical practice, and reported that removal of dental amalgam fillings, when combined with additional treatment, significantly reduced symptoms associated with chronic mercury toxicity (CMT). A

diagnosis of CMT was made on the basis of identified mercury exposure, typical multi-system symptom profile, clinical signs and, when possible, a positive dimercapto-propane-sulphonate (DMPS) urine mercury test (>50 μg Hg/g creatinine). Removal of dental amalgam only (no additional treatment) did not significantly affect outcome scores. Removal of amalgam, coupled with a 3 month course of chelation therapy with dimercapto-succinic acid (DMSA), and nutrient and antioxidant support (not defined), or removal of amalgam accompanied with homeopathic therapy (not defined), was associated with reductions in symptom scores, and scores for fatigue, memory loss and depression. Apolipoprotein-E (Apo-E) genotyping was performed on a subset of subjects where significant positive correlations were reported for the Apo-E3/4 and E4/4 genotypes and CMT, Alzheimer's disease, bipolar mood disorder and extreme depression (Chi square tests). Since symptom improvement was only seen in groups with combined amalgam removal and substantial concomitant therapy, which was not well defined, it is not possible to determine if amalgam contributed to the symptoms. The Apo-E findings are clearly suggestive of an association with specific clinical entities, but their relationship to mercury exposure remains unclear.

Zimmer et al. (2002) determined the internal mercury exposure of two groups differing in their attitude towards possible health hazards associated with mercury from amalgam fillings. They sought to examine whether the two groups differed with regard to the mercury concentration in different biological matrices and to compare the results with current reference values. Blood, urine, and saliva samples were analyzed from 40 females who claimed to suffer ill health from amalgam fillings (amalgam-sensitive subjects) and 43 female control subjects who did not claim any such association (amalgam-nonsensitive subjects). For amalgam-sensitive subjects, median (range) mercury concentrations in blood were 2.35 (0.25–13.40) μg/L, and for nonsensitive subjects, 2.40 (0.25–10.50) μg/L. In urine, the median mercury concentrations were 1.55 (0.06–14.70) μg/g creatinine [2.01 μg/L] for amalgam-sensitive subjects and 1.88 (0.20–8.43) μg/g creatinine [2.44 μg/L] for nonsensitive subjects. No significant differences in blood or urinary mercury concentrations could be found between the two groups. Mercury concentrations in blood and urine of the examined subjects were within the range of background concentrations in the general population, including persons with amalgam fillings. Compared with persons without amalgam fillings, mercury concentrations were increased in blood and urine by a factor of three and five, respectively. Mercury concentrations in saliva did not correlate with the concentrations in blood and urine but did correlate with the number of amalgam fillings or filling surfaces. The authors concluded saliva is not recommended for biological monitoring.

Summary of reports on human nervous system

Some reports in this section suggest that removal of dental amalgam can lead to improvement in clinical complaints in some patients; however, in these cases, substantial concomitant interventions (antioxidants, nutritional supplements, increased contact with medical personnel) were necessary, and amalgam removal alone did not significantly improve symptoms. In light of other reports showing significant placebo effects in persons believing that dental amalgams contribute to their maladies, it is possible that symptom improvements reported to accompany amalgam removal are also either part placebo effect or are benefits related to concomitant

treatments. The observations that tissue and/or urinary mercury concentrations have been found to be no different between 'sensitive' and 'nonsensitive' persons suggests that inorganic mercury exposures from dental amalgam do not contribute to adverse effects, including Alzheimer's disease. Alternatively, it is possible that some persons are more sensitive to the adverse effects of mercury than is the population at large. Where correlations between blood mercury concentrations and severity of Alzheimer's disease were noted, the source of the blood mercury was not reported and blood mercury concentrations were all within the range found in the general population.

While in one report, hair mercury concentrations (generally indicative of organic mercury exposure) of autistic children were found to be significantly lower than those of non-autistic children, suggesting differences in mercury excretion and/or metabolism, a meta-analysis of over 20 years of literature concluded that the epidemiological evidence shows that low-level mercury exposure is not a cause of autism (relative risk = 0.49). Thus the weight of evidence would suggest dental amalgam exposures do not contribute to autism.

Human Immune System (8)

Kanerva et al. (2001) in a multi-center, retrospective study of persons with suspected contact reactions of the oral mucosa or lips, or suspected occupational and non-occupational contact reactions caused by dental products, approximately 13% of 767 participants exhibited a positive reaction to a patch test with dental screening series.

Laeijendecker et al. (2004) showed that contact allergy to mercury compounds can be involved in the pathogenesis of oral lichen planus, especially if there is close contact with amalgam fillings. In persons with a positive patch test to mercury compounds, partial or complete removal of amalgam fillings was reported to result in significant clinical improvement of the oral lesions.

Marcusson & Jarstrand (1998) described a study of 22 patients experiencing malaise following removal of old amalgams and 15 healthy controls. Based on their psychosomatic response to challenge with percutaneously-administered, low dose metallic mercury and phenyl mercuric acetate, patients were divided into two groups: 12 patients with a high score (mercury intolerant patients) and 10 with a negative or low score (mercury-tolerant patients). Neutrophils from participants were exposed in vitro to mercuric chloride and phenyl mercuric acetate in increasing concentrations and the superoxide anion production was measured. A significant difference in the amount of superoxide anion production in unstimulated neutrophils was found between the tolerant and intolerant patients for one concentration of mercuric chloride. The authors suggest that whatever the mechanism, the findings may explain why some patients react with psychosomatic symptoms to low doses of mercury.

Marcusson et al. (2000a) reported a comparison of the activities of the scavenger enzymes glutathione peroxidase, superoxide dismutase, and catalase in phagoctyes from mercury

tolerant and intolerant patients. They also evaluated superoxide anion responses and enzyme activity in relation to patient psychomatic score. No significant differences were found in the mean values of enzyme activity, even though the mean value of superoxide dismutase was higher in the intolerant patient group than in the tolerant group and catalase activity was lower in the tolerant patients than in the controls. The authors suggest that the lower superoxide anion production observed in mercury-intolerant patients could be the result of an increased superoxide dismutase activity which was stimulated due to chronic mercury exposure or that superoxide generation upon mercury exposure is genetically determined in the different patient groups.

Marcusson et al. (2000b) followed their earlier studies using blood cells obtained from mercury tolerant and intolerant patients, and determined whether mercuric chloride could stimulate lymphocytes *in vitro* to produce serotonin. By utilizing phytohemagglutinin as a stimulatory substance, mercuric chloride could induce the release of serotonin in a concentration-dependent way. When the cells were challenged with mercuric chloride alone there was a significant difference between the tolerant patients and the controls but no differences between the other combinations. The results did not support the concept of mercury tolerance and mercury intolerance.

Prochazkova et al. (2004) studied patients with autoimmune and allergic diseases (systemic lupus, multiple sclerosis, autoimmune thyroiditis, and atopic eczema) whose lymphocytes showed stimulation by low doses of inorganic mercury in vitro. The patients often reported clinical metal sensitivity, especially to nickel. Using an optimized lymphocyte stimulation test, the health impact of amalgam replacement was studied in 35 mercury-allergic patients whose amalgam fillings were replaced with composites and ceramic materials. Follow-up health status and lymphocyte reactivity were assessed and evaluated 6 months after amalgam removal. Results indicated that in vitro reactivity to inorganic mercury, silver, organic mercury, and lead after the replacement of amalgam decreased significantly. Of 35 patients, 25 (71%) showed improvement in health. The remaining patients exhibited either unchanged health (6 patients, 17%), or worsening of symptoms (4 patients, 11%). The highest rate of improvement was observed in patients with multiple sclerosis, and the lowest rate was noted in patients with eczema. The authors conclude that mercury-containing amalgam may be an important risk factor for mercury-sensitive patients with autoimmune disease.

Valentine-Thon et al. (2006) tested 700 patients with clinical suspicion of metal sensitization using a MELISA (Memory Lymphocyte ImmunoStimulation Assay) LTT (Lymphocyte Transformation Test) and found that ~75% responded to one or more metals. Reactivity was most frequent to nickel (~68%), cadmium (~24%), gold (~18%) and palladium (~13%). Reactivity to inorganic mercury was ~11%. While no metal exposure histories were provided, the incidence of mercury allergy in affected (symptomatic) persons is similar to that reported by Kanerva et al. (2001).

Yaqob et al. (2006) evaluated the clinical relevance of a MELISA® (an optimized lymphocyte proliferation test) for assessing metal-induced inflammation in 513 patients with symptoms

similar to chronic fatigue syndrome, including muscular-skeletal pains, gastrointestinal disturbances, hormonal perturbations, psychological symptoms, and chronic fatigue. Lymphocyte reactivity was studied in vitro from samples collected prior to and after replacement of biologically incompatible dental restorations. The presence of metal-reactive lymphocytes was evaluated by calculating a Stimulation Index. Nickel was the most common sensitizer whereas inorganic mercury was second. Patients were treated with replacement of amalgams and other restorative materials containing metals to which their lymphocytes were reacting and antioxidant treatment. When indicated, some patients also received steroids. Replacement of reactive dental materials down-regulated lymphocyte metal-specific responses in vitro and was associated with improvement in the health status of patients. The reduced ability of lymphocytes to respond to metals in vitro after dental metal replacement was attributed to a decrease in chronic inflammation in vivo. The authors suggest that in vitro testing improves diagnosis and is useful for monitoring the outcome of treatment.

Summary of reports on human immune system

Thirteen percent of persons with suspected contact reactions of the oral mucosa or lips or suspected occupational and non-occupational contact reactions caused by dental products exhibited a positive reaction to patch test with a dental screening series. Reactivity was most frequent to nickel (~68%); reactivity to inorganic mercury was ~11%. The percent of the general population having such contact reactions was not reported. Contact allergy to mercury compounds can be involved in the pathogenesis of oral lichen planus and several possible mechanisms including alterations in superoxide dismutase activity are under investigation. To the extent that allergens can exacerbate pre-existing conditions such as autoimmune disease, mercury-containing amalgam may exacerbate these conditions in persons with allergies to mercury. In persons with a positive patch test to mercury compounds, partial or complete removal of amalgam fillings has been reported to result in significant clinical improvement of oral immune-related lesions, such as oral lichen planus.

Human Occupational Exposure (12)

Counter et al. (2006) conducted neurocognitive assessments of 73 children of Andean (Nambija and Portovelo areas) gold miners using Raven's Colored Progressive Matrices (RCPM) test of visual-spatial reasoning. The mean urinary mercury concentration obtained from 53 of the subjects was 13.3 µg/L [10.2 µg/g creatinine]. The report indicates that a substantial number of children in the Nambija area have neurocognitive deficits. Sources of mercury included elemental mercury vapor from the gold amalgamation process and methylmercury from fish and other animals in the study area. No mention of amalgams was made. The authors proffer that it is possible that other industrial and environmental contaminants (e.g., arsenic, cadmium, and sodium cyanide found in the study areas) may have confounded their findings. The ages of the children studied ranged from 5 to 8 years; however, the duration of exposures was not reported. The finding that adverse effects were only seen in children from Nambija and not Portovelo suggest a possible location bias.

Efskind et al. (2006) conducted a case-controlled, cross sectional study of 49 occupationally exposed chloralkali workers and 49 age-matched controls; no effect of previous exposure to mercury vapor on kidney function was observed. Workers had been exposed to mercury vapor an average of 13 years; exposure had ceased an average of 4.8 years prior to analyses. This study suggested that increased urinary NAG (N-acetyl-beta-D-glucosaminidase) concentrations reported previously may be reversible upon cessation of exposure. Urinary mercury was 1.7 nmol Hg/mmol creatinine [3 μg/g creatinine; 3.9 μg/L] in the previously exposed subjects compared to 1.2 nmol Hg/mmol creatinine [2.1 μg/g creatinine; 2.7 μg/L] in the control group.

Haut et al. (1999) describe comprehensive neuropsychological and emotional functioning in a group of 13 workers exposed to inorganic mercury vapor over a 2- to 4-week period compared to a normal control group. The mercury was contained in paint and vaporized by oxyacetylene cutting torches as workers cut through sheet metal. After exposure, all patients had elevated blood mercury concentrations with an average of 48.7 μg/L and a range of 21 to 84 μg/L (normal <20 μg/L). Air samples taken after exposure ended found air concentrations up to 80 $\mu g/m^3$. [American Conference of Governmental Industrial Hygienists recommended a Threshold Limit Value-Time Weighted Average of 25 $\mu g/m^3$ in 2001.] Evaluations were conducted from 10 to 15 months after termination of exposure. Emotional problems included increased focus on physical functioning, depression, anxiety, and social withdrawal. Observed cognitive deficits included impairment in motor coordination, speed of processing with and without a motor component, cognitive flexibility, verbal fluency, verbal memory, and visual problem solving and conceptualization.

Hurtado et al. (2006) reported on Peruvians persons working in or living near highly contaminated, gold mining and processing operations. Urinary mercury concentrations averaged 728, 113, 18, 8 and 4 μg/L, respectively, for persons working in smelters, living near smelters, working in gold amalgamation, living in the mining town but not participating in mining activities, and living outside of the town. This article did not address health effects.

Iwata et al. (2007) evaluated a group of 27 Chinese miners and smelter workers who had high concentrations of exposure to mercury vapor and produced urinary mercury concentrations averaging 228 μg/g creatinine [296 μg/L]. A comparison group of 52 unexposed subjects (mean urinary mercury concentration of 2.6 ug/g creatinine [3.4 ug/L]) was used to compare metrics of tremor and postural sway. Tremor intensity was significantly greater in the exposed group, but there were no significant differences between the two groups in any of the postural sway parameters. The authors suggest that hand tremor is the metric more sensitive to Hg vapor exposure.

Kobal et al. (2000) investigated renal damage in 45 mercury miners under conditions of relatively short low-level exposure to elemental (metallic) mercury vapor. The average duration of exposure was 37 (6–82) days. Before exposure, mean urinary mercury concentrations were 18.5 μg/g creatinine [24 μg/L] and after were 69.9 μg/g creatinine [90.9 μg/L]. Immunoelectrophoretic changes in the composition of urinary proteins occurred after

exposure in 22 of the 45 miners, suggestive of slight glomerular and tubular damage in at least one-half of the miners.

Lindbohm et al. (2007) conducted a retrospective, questionnaire-based study of 222 miscarriages and 498 controls evaluating occupational exposure to chemicals in dentistry and possible association with miscarriage. No strong association or clear dose-response relationship between occupational exposure to chemical agents or restorative materials and the risk of miscarriage was observed. A slight but non-significant increase in risk was found for exposure to some acrylate compounds, mercury amalgam, solvents and disinfectants leading the authors to conclude that they could not rule out the possibility of a slightly increased risk of miscarriage among exposed dental workers.

MacLehose et al. (2001) describe an incident where spillage of elemental mercury led to widespread contamination of 225 individuals and confirmed toxicity in 19. Of the 225 affected individuals identified, 37 were found to have concentrations of mercury in their blood or urine that put them at risk. For example, a 15-year-old male had a blood mercury concentration of 329 μg/L; he was hospitalized and treated with DMPS. [A typical blood total mercury concentration in an adult population (> 1000 subjects) with an average number of amalgam restorations from a study reported in the 2006 White Paper is 2.55 μg/L]. His urinary mercury concentrations reached a high of 2037 μg/L on day 22, and 10 months later, his urinary mercury concentrations were 10 μg/L. A 37-year-old woman had a blood mercury concentration of 178 μg/L on day 15 but was admitted to hospital on day 27 because of the severity of her symptoms. Mercury concentrations were monitored for all at-risk individuals, and the incident was closed 15 months after the original incident. The authors note that the lack of evidence-based guidelines for nonoccupational biological and environmental monitoring made the incident difficult to manage and follow up.

Maksimovic et al. (2004) obtained blood samples for hematological analyses from workers involved continuously for an average of 8.4 years, periodically for an average of 7.7 years, or earlier for 10.3 years (but at least 5 years since their last exposure), in the production of chlorine using the mercuric electrolysis method, and from 38 control workers (not exposed to mercury vapor). Urinary mercury concentrations were 0.379, 0.103, 0.045 and 0.015 μmol/L, respectively, for the four cohort groups. [These urinary mercury concentrations are equivalent to 76, 21, 9, and 3 μg/L and 59, 16, 7, and 2 μg/g creatinine]. In the groups exposed to mercury vapor, there was a significant increase in erythrocyte count and a concomitant decrease in mean corpuscular volume (MCV). In addition the mean values for hemoglobin concentration, mean corpuscular hemoglobin concentration (MCHC) and the platelet counts were also higher, but not significantly. There were no differences in hematocrit, mean corpuscular hemoglobin (MCH), and leukocyte counts.

Vimercati et al. (2001) followed up on earlier reports that showed reduction in tumor necrosis factor-α (TNF-α) serum concentrations in workers with prolonged exposure to low doses of inorganic mercury, suggesting an in vivo functional defect of the monocyte-macrophage system. In this report, the authors evaluated whether workers exposed to lower doses of inorganic

mercury demonstrated changes in the monocyte-macrophage system and effects on polymorphonuclear leukocyte (PMNL) chemotaxis. The monocyte-macrophage system and natural killer (NK) cells were examined in 19 exposed workers (from a fluorescent light bulb factory) and 25 unexposed control workers. Mercury concentrations in urine were significantly higher in workers than in controls (9.7 ± 5.5 μg/L [7.5 μg/g creatinine] and 2.4 ± 1.2 μg/L [1.8 μg/g creatinine], respectively). When workers were considered as a whole (exposed plus controls), no correlation was found between current urinary mercury concentrations and any immunological parameters. However, when exposed workers were studied separately, an inverse correlation was observed between cumulative mercury exposure and cells expressing the CD13 and CD15 molecules, and NK cells. A significant impairment in PMNL chemotaxis was also observed in exposed workers. The study suggests that chronic exposure to metallic mercury led to subtle impairments in circulating monocyte and NK cells and in PMNL chemotactic function in this group of workers, even though they remained clinically asymptomatic.

Wastensson et al. (2006) studied tremor in 43 mercury vapor-exposed chloralkali workers and 22 age-matched controls, and quantitative tremor assessment did not indicate an effect of mercury exposure. The median urinary mercury concentration for workers exposed an average of 15 years was 5.9 μg/g creatinine [7.7 μg/L] and for referents it was 0.7 μg/g creatinine [0.9 μg/L]. No associations were found with current or cumulative mercury exposure for the majority of the tremor measures. There were indications that exposure to mercury vapor was associated with a lowering of the tremor frequency in the non-dominant hand and a possible interaction with smoking, but the differences were small. Overall, this study indicates no significant adverse effects on tremor at these exposure levels.

Zabinski et al. (2000) assessed the influence of occupational exposure to mercury vapor on the activity of red blood cell enzymes, on peripheral blood indices, and on serum concentrations of iron, ferritin, transferrin, and total iron binding capacity. Studies were carried out on 46 men aged 21–56 exposed to mercury vapor during periods of work ranging from 7 months to 32 years. The control group consisted of 35 healthy workers not exposed to chemical or physical agents. The results indicated that long-term exposure to mercury vapors induces changes in the activity of red blood cell enzymes and may also influence other important hematological parameters of the peripheral blood. The authors postulated that a substantial increase in ferritin levels supports the notion that it possesses detoxifying properties against mercury.

Summary of reports on human occupational exposure

Occupational exposures to mercury vapor can be very high and lead to concomitantly high tissue and urinary concentrations, most of which are not relevant to exposures associated with dental amalgam mercury. Several studies reviewed in this section evaluated occupational cohorts exposed to high levels of mercury vapor, where urinary mercury concentrations were one or two orders of magnitude higher than the average population values of 1-4 μg Hg/L, including individuals with amalgams. [In the 2006 FDA White Paper, five studies that were reviewed also confirmed that, in the general population that is not occupationally exposed to

mercury, average urinary mercury values are in the range of 1-3 µg/g creatinine (1.3-3.9 µg/L) (Factor-Litvak et al., 2003; Bellinger et al., 2006; DeRouen et al., 2006; Kingman et al., 1998; Dye et al., 2005)]. Further, in the 2006 White Paper, two studies of dental professionals who placed amalgam restorations reported average urinary Hg concentrations also 2-3 µg/g creatinine (Woods et al., 2005; Echeverria et al., 2005)]. Protracted exposures to high levels of mercury vapor resulting in urinary mercury concentrations above those health-protective threshold concentrations associated with subtle neurological and renal health effects (see FDA White Paper, 2006) can lead to a variety of adverse effects in including neurocognitive deficits that can last long after cessation of exposure, hand tremor, renal damage, and alterations in hematological and immunological parameters. In dental professionals, no strong association or clear dose-response relationship between occupational exposure to chemical agents or dental restorative materials and the risk of miscarriage was observed but the possibility of a slightly increased risk of miscarriage among exposed dental workers could not be ruled out.

Human Pharmacokinetics/Body Burden (20)

Aposhian (1998) used DMPS as a chelating agent to mobilize mercury and quantify urinary mercury in a study involving subjects with and without dental amalgams. Those without dental amalgams excreted significantly less than those with dental amalgams (5.1 versus 17.6 µg Hg over 9 hours). In urine collected over nine hours prior to chelation, urinary excretion of mercury was 0.27 µg and 0.70 µg for persons without and with amalgam, respectively. The authors posited that two-thirds of the mercury excreted in persons with amalgams was derived from their amalgams. In a comparison of dentists, dental technicians, and a control group, DMPS treatment led to 49-, 88- and 35- fold increases in urinary mercury excretion, respectively. Measurement of urinary mercury output after mobilization of mercury via DMPS may provide a better assessment of mercury body burden than pre-mobilization urinary mercury concentrations.

Archbold et al. (2004) utilized the chelator DMSA to mobilize mercury in 14 healthy subjects with Hg amalgams. The increase in urinary mercury in these subjects was of the same order reported by others for individuals presumably symptomatic to the adverse effects of mercury. One of the 14 subjects in the present study also suffered serious side effects from the DMSA loading. These authors questioned the value of oral chelation tests.

Dunn et al. (2008) reported on the mercury content in scalp hair and urine in children from the New England Children's Amalgam Trial (NECAT). The study population was comprised of 534 children, aged 6 to 10 years, in a two-armed, prospective randomized safety trial study that was designed to compare the neuropsychological and renal function of children whose dental restorations were composed of mercury amalgam with those whose restorations were non-mercury free. Measurements were taken at baseline (prior to the placement of dental restorations) and for 5 years after placement. Fish consumption was a highly significant predictor of mercury concentrations found in hair whereas amalgam placement did not affect hair concentrations of mercury. Across all study years, hair mercury concentrations ranged from an average of about 0.25 µg/g in children who ate fish less than once per month to 0.9

µg/g in children with daily fish consumption. The number of mercury amalgams was positively associated with urinary mercury concentrations and the daily use of chewing gum in the presence of amalgam was associated with increased urinary mercury concentrations. Across all study years, urinary mercury ranged from an average of about 0.5 µg/g creatinine [0.65 µg/L] in children with no mercury amalgam, to about 2.8 µg/g creatinine [3.64 µg/L] in children with 16 or more dental amalgam fillings. In general, urinary concentrations are thought to relate more to inorganic mercury intake, whereas hair concentrations are thought to relate more to organic mercury intake.

Ely et al. (1999) examined urinary mercury excretion in 18 subjects whose urine porphyrin patterns were highly abnormal. Enrollment required that subjects have at least 5 occlusal amalgams and currently suffer signs and symptoms associated with 'micromercurialism' (MM), a non-specific condition, comprising such symptoms as lethargy, tremor, gingivitis, labile pulse, tachycardia, and hematologic changes. Subjects exhibited a variety of disorders including Alzheimer's disease, ataxia, premenstrual syndrome, severe depression, eating disorder, allergies and others. When urinary mercury values were expressed as µg Hg excreted/day, rather than µg/L, a bimodal distribution of daily mecury excretion was observed. Given the small number of subjects and the very disparate health conditions of the participants, the findings from this study are difficult to interpret.

Ely (2001) reported the amount of mercury vapor released from amalgams in two subjects before and after chewing stimulation, and measurements were accomplished using a portable battery powered mercury vapor analyzer. Values before chewing ranged from 0 to 11 µg/m^3 and after chewing from 5 to 43 µg/m^3, depending upon the oral quadrant and tooth number involved. The author suggests that the more recent amalgams with higher copper content release mercury faster than do older amalgams.

Engqvist et al. (1998) examined the speciation of mercury excreted in feces in a study of six individuals with amalgam fillings and found that most of the mercury excreted consisted of oxidized mercury (Hg^{2+}), probably bound to sulfhydryl-containing compounds. The proportion of amalgam excreted in feces as amalgam particles (APs) did not exceed 26% of the total amount of mercury excreted. In two subjects that consumed mercury as a Hg-cysteine complex (oral exposure), mercuy vapor inhalation, and mercury from APs (oral exposure), 80% of the mercury from APs and mercury bound to sulfhydryl groups was excreted and 40% of the mercury vapor was excreted in feces. The background excretion of mercury in feces was greater in the subject with the most (60) dental amalgam surfaces (47 µg/24 hours) than in subjects with no amalgams (2 and 4 µg/24 hours) and in a subject with 30 amalgam surfaces (25 µg/24 hours).

Guzzi et al. (2006) examined total mercury concentrations in autopsy tissue from 18 subjects and found that total mercury concentrations were significantly higher in subjects with a greater number of occlusal amalgam surfaces in all types of tissue (brain, thyroid and kidney). Brain tissue mercury concentrations were significantly higher than thyroid or kidney concentrations in subjects with more than 12 occlusal amalgam fillings but not in those with 3 or less. No

history of other mercury exposures was presented. The authors note that they did not replicate the work of others that showed higher concentrations of mercury in the pituitary than cortex.

Halbach and Welzl (2004) reported on an *in situ* method for measuring real-time low-level, intraoral mercury vapor exposure from dental amalgam that appears to be an improvement over controversial analytical techniques attempting to estimate mercury release from amalgam. The method involves a pump, magnetic valves, an electronic flow controller, and a handle with a disposable mouthpiece for aspiration of oral air, connected to an atomic absorption spectrometer for mercury analysis. Two subjects with dental amalgams were tested using the method, and oral mercury vapor concentrations were measured before and after chewing stimulation. The method was sufficiently sensitive to detect increases in mercury vapor after chewing; the amounts released immediately after chewing (~100 ng/min) decreased to background concentrations (~25 ng/min) with half-times of 10.7 and 8.6 minutes. The authors suggest this method should be useful in much larger populations.

Hansen et al. (2004) evaluated the release of mercury from amalgams in a study of 2223 subjects using a newly developed chewing gum test. This procedure was employed as part of a standardized Mercury Triple Test which measured mercury in hair and urine (before and after mobilization with DMPS) and mercury released from dental fillings to obtain measures of mercury body burden. 50^{th} centiles were 1.7 µg Hg/g creatinine [2.2 µg/L] in urine prior to DMPS treatment; 57 µg Hg/g creatinine [74 µg/L] after treatment with DMPS; 454 ng Hg/g hair; and ~ 1 µg Hg/min of chewing gum. Mercury concentrations in chewing gum and in urine after treatment with DMPS correlated with number of amalgams. Hair mercury concentrations were considered difficult to align with either urine or gum concentrations, perhaps due to exogenous sources of mercury and varying lengths of hair utilized. The authors report that for many subjects the amount of mercury released from dental amalgams during chewing determines whether the weekly mercury intake lies below or above the provisioned tolerable weekly intake (PTWI) of 5 µg Hg/kg (WHO). While weekly mercury intake in most subjects will be well below the PTWI, for patients with a large number of fillings, the PTWI may be exceeded; for example, persons exceeding the 75^{th} centile value in chewing tests would exceed the PTWI by 46%. The authors suggest that the Mercury Triple Test provides a reliable diagnostic tool for evaluating the degree of mercury exposure in individuals. No health outcomes were reported.

Khordi-Mood et al. (2001) reported urinary mercury concentrations in 43 children ages 5 to 7 years before and after posterior amalgam placement. Urinary mercury concentrations before and after amalgam placements were 3.04 ± 1.42 µg/L [2.34 µg/g creatinine) and 4.20 ± 1.60 µg/L [3.23 µg/g creatinine], respectively. The respective results after adjustment for specific gravity (SG) were 3.83 ± 2.54 µg/L and 5.14 ± 3.14 µg/L (p=0.001). The study suggests mercury from amalgam is absorbed systemically and contributes to urinary mercury excretion. No significant correlation was found between urinary mercury excretion and the number of teeth filled or filled surfaces. The authors suggest that more refined studies are required to elucidate any possible health effects of amalgam fillings.

Krauss et al. (1997) studied mercury content in saliva of 20,000 subjects and reported that in this population, the mean number of amalgam fillings was 9 and the median mercury concentration was 11.6 ug/L [8.9 ug/g creatinine] in pre-chewing saliva and 29.3 ug/L [22.6 ug/g creatinine] in saliva after chewing. Calculations suggest that in about 30% of subjects the provisional tolerable weekly intake (PTWI) of mercury is exceeded. No health outcomes were reported.

Krone et al. (2002) described a method for measuring mercury vapor using a portable, battery-powered, hand-held instrument (the Jerome 411 Mercury Vapor Analyzer) that provides a digital display of mercury concentrations in 10 seconds. They propose that it can be useful for identifying high mercury-release restorations. Oral mercury vapor concentrations were obtained from 11 staff and patients at a nursing home and 31 people attending a lecture. Testing protocols included chewing stimulation, drying the teeth, and suspension of breathing during sampling. In the nursing home group, baseline mercury flux ranged from 0 to 0.056 mg/m^3. The median was 0.0035 mg/m^3 and nearly 80% of the measurements were below 0.011 mg/m^3, consistent with results of several other studies. Chewing stimulation increased mercury release, generally by two- to three-fold; however, some amalgams were reported to exhibit more than a 12-fold increase. In the lecture attendee group, one-third of the oral mercury vapor readings were above 0.050 mg/m^3 after chewing stimulation. The highest concentration measured in one amalgam was 0.211 mg/m^3. The authors refer to a model that suggests teeth grinding, mouth breathing, and high-copper amalgam restorations significantly increase mercury vapor release, and suggest that the instrument be used to identify high Hg-release restorations.

Leistevuo et al. (2001), using data from a group of 187 persons with and without amalgams, reported that in persons with amalgam, methylmercury concentrations in saliva (mean 14 nmol/L) were significantly higher than in persons without amalgams (mean ~3 nmol/L). The authors suggest that methylmercury is formed by bacteria in the oral environment of some persons. No health outcomes were reported.

Lindh et al. (2001) studied 25 women and 2 men with health problems reportedly associated with dental amalgams and a healthy control group. Metal concentrations in plasma were determined and nuclear microscopy of isolated individual blood cells was performed. Significant increases in copper, iron, zinc, and strontium were found in patient plasma. There was no significant difference in plasma selenium between the patients and control groups. In erythrocytes, a significant increase in calcium and a significant decrease in magnesium, copper, manganese, and zinc were found. Calcium, magnesium, manganese, and copper increased in patient neutrophil granulocytes and zinc decreased. A conspicuous finding was the presence of measurable mercury in a few of the cells from the patient group but not in the control group. The authors suggest that nuclear microscopy of isolated individual blood cells might provide a better diagnostic tool for metal exposure than blood/plasma measurements.

Lygre et al. (1999) measured the content of mercury and silver in saliva of persons with amalgam fillings and sought to determine if amalgam particles were present in samples of

stimulated saliva to determine the influence of the particles on the mercury concentrations obtained. Fifty-three patients with a wide range of complaints self-related to their amalgam fillings were examined. Stimulated saliva was collected from each patient and analyzed for silver and mercury, the concentrations of which correlated with the amount of amalgam present. There was a strong correlation between mercury and silver concentrations. Considerable amounts of mercury and silver were present as amalgam particles; thus, the authors concluded that the presence of amalgam particles in saliva should be controlled when determining mercury concentrations in saliva from subjects with amalgam fillings.

In a report from DHHS/Center for Disease Control and Prevention (National Center for Environmental Health and Centers for Disease Control, 2005), 148 chemicals and metabolites were measured in blood and urine samples from a random sample of participants in the National Health and Nutrition Examination Survey (NHANES). Total mercury measurements in blood and urine include contributions from organic and inorganic forms. Measurements were provided for various demographic groups - ages 1-5 (females and males), ages 16-49 (females only), and for three ethnic/race categories – with sample sizes ranging from 370-1960. Mean urinary concentrations for all groups ranged from 0.522 to 0.710 µg/g creatinine [0.68 to 0.92 µg/L]; mean blood concentrations ranged from 0.307 to 1.35 µg/L. The report showed that all women of child bearing age had blood mercury concentrations below 58 µg/L, a concentration associated with neurological effects in the fetus. The report also showed that 5.7% of women of child bearing age had urinary mercury concentrations between 5.8 and 58 µg/L and suggest that better defining safe concentrations of mercury in maternal blood is a priority area for additional research. No health outcomes were reported.

Sandborgh-Englund et al. (1998) examined mercury concentrations in blood, plasma and urine following amalgam removal in 12 case reports. A transient increase in mercury concentrations was noted in blood and plasma (32% increase) within 48 hours after amalgam removal but no increase in urinary mercury concentrations was noted. In plasma, the median half-life of mercury elimination was estimated to be 88 days and for urine 46 days. Mercury concentrations in blood, plasma and urine all declined after amalgam removal and slowly approached those of subjects with no history of amalgam fillings. No health outcomes were reported.

Wilhelm et al. (2006) reported revised reference values for the environmental pollutants arsenic, cadmium, lead and mercury in Germany. Reference values represent the 95th percentiles for blood or urinary concentrations which are obtained by continuously monitoring population concentrations. Interim values for mercury for 6- to 12-year-old children were determined in 2005 to be 1.5 and 1.4 µg/L, for blood and urine, respectively. The current report revises those concentrations to be 1.0 µg/L for blood and 0.7 µg/L for urine in children without amalgams. The data indicate decreasing exposure to mercury in this population. No health outcomes were reported.

Woods et al. (2007) studied a group of 507 children, 8 to 10 years old, from the Portugal children's prospective, randomized clinical study of the effects of dental amalgam in children.

Urinary mercury concentrations were followed longitudinally for 7 years and related to number of amalgam fillings. Baseline (prior to placement of dental restorations) urinary mercury concentrations (mean of 1.5 μg/L; ~ 1.05 μg/g creatinine) increased to a maximum of 3.2 μg/L [~ 2.24 μg/g creatinine] at year 2 and then declined to baseline or near baseline concentrations by year 7. There was a strong positive relationship between urinary mercury concentrations and both number of amalgam surfaces and time since placement: the greater the number of amalgam surfaces, the greater the urinary mercury concentrations; the longer the time since amalgam placement, the lower the urinary concentrations. Girls were found to excrete significantly more mercury (higher concentrations in urine) than boys with comparable treatment and thus it was suggested that there was a sex-related difference in the handling of mercury, with males perhaps having a higher body burden than females because they excrete less mercury. Body weights were not considered and no measurement of mercury body burden was made.

Zhang et al. (2007) studied amalgam tattoos and explored (1) the tissue distribution of the metallic substances contained in amalgam, (2) the specific association of the electron-dense deposits with intracellular and extracellular structures, and (3) their elemental composition using x-ray microanalysis. An amalgam tattoo refers to the distinct pigmentation of the oral mucosa resulting from accidental incorporation of dental amalgam into soft tissues. In this study, 17 oral amalgam tattoos were examined by transmission electron microscopy and energy dispersive x-ray microanalysis. Elemental analyses regularly revealed the presence of silver, sulphur, copper, and lead in the tattoo decay products. The authors were unable to detect all four main elements of amalgam (copper, silver, tin, and mercury) together and did not detect tin at all. Mercury was found in only one inclusion. The authors suggest they did not generally find mercury in amalgam tattoos because it is degraded and released. They believe element spectroscopy facilitates a differential diagnosis between amalgam tattoos and cancer.

Summary of reports on human pharmacokinetics/body burden

In general, several studies evaluated in this Addendum, the FDA White Paper, and other reviews demonstrate a correlation between mercury concentrations in either urine, feces, saliva, or tissue (including cadaver tissues) and the number of amalgams; however, in most studies reviewed above, no health outcomes are reported. Urinary concentrations of mercury in children were approximately the same as those reported in the New England and the Portugal Children's Trials published in 2006 (~ 1-3 ug Hg/g Cr). In both of those prospective, randomized clinical trials on the effects of mercury amalgam in children, it was shown that the number of mercury amalgam restorations had a significant dose-response relationship with urinary mercury concentrations. It was also shown in one of these studies reviewed in the section above that the number of mercury fillings did not affect concentrations of mercury in hair, but that hair mercury concentrations were correlated with fish consumption. The other study showed that females had higher urinary concentrations of mercury (excreted more) than males, suggesting sex differences in mercury disposition. Urinary mercury concentrations in both studies returned to baseline (pre-amalgam placement) concentrations within 7 years.

Chewing, teeth grinding, and mouth breathing can increase mercury vapor release. Blood and plasma Hg concentrations increase transiently after amalgam removal, but no associated increases in urinary Hg concentrations were noted. Measurement of urinary mercury output after mobilization (chelation) via DMPS or DMSA may provide a better assessment of mercury body burden than pre-mobilization urinary mercury concentrations.

Human Susceptible/Sensitive Subpopulations (5)

Barregard et al. (2008) reported on the renal effects of mercury amalgam in children from the New England Children's Amalgam Trial (NECAT). Five hundred and thirty four children, aged 6 to 10 years, comprised the population from this two-armed, prospective randomized safety trial study that was designed to compare the neuropsychological and renal function of children whose dental restorations were composed of mercury amalgam with those whose restorations were non-mercury materials. Measurements were taken at baseline (prior to the placement of dental restorations) and for several years (up to 5) after placement. For this study, primary outcomes evaluated were urinary excretion of biomarkers of tubular and glomerular kidney function including: urinary excretion of albumin, alpha-1-microglobulin, gamma-glutamyl transpeptidase, and N-acetyl-β-D-glucosaminidase. There were no effects of mercury amalgam on any of the renal tubular markers but there was a significantly increased prevalence of microalbuminuria (MA) in children in the amalgam group in years 3 and 5. This effect was not related to the number of amalgam fillings or to urinary mercury concentrations except during year 5 when there was an association with urinary mercury concentrations. The significance of this observation is not known and was suggested as a possible random observation needing additional assessment.

Custodio et al. (2005) compared blood, plasma and urinary mercury concentrations in adult males occupationally exposed to mercury vapor (gold miners, n = 99 and buyers, n = 37) with those of a referent (control) group (n = 73). Polymorphisms in glutamyl-cysteine ligases (GCL) and glutathione S-transferases (GST) were examined with respect to mercury retention, since these enzymes mediate glutathione (GSH) production which facilitates mercury excretion as GSH-Hg conjugates. The presence of the GCLM-588T allele was associated with increased blood, plasma and urinary mercury concentrations, suggesting that genotypes with decreased GSH availability for mercury conjugation affect the metabolism of inorganic mercury. The finding that this effect of the GCLM allele was only conspicuous in one of the assessed groups makes interpretation of the findings very difficult.

Godfrey et al. (2003) evaluated records of 400 persons seen at two primary health clinics, all of whom had histories and/or symptoms and signs (determined by questionnaire) that were presumptive of chronic accumulative exposure to mercury. A mercury challenge test (treatment with the chelator, DMPS) was administered to 150 subjects for determination of mercury urinary excretion. Apo-E genotyping has been investigated as a possible indicator of susceptibility to heavy metal neurotoxicity. Of the initial 400 patients, the majority (~88%) had the Apo-E 3/3, 3/4 or 4/4 genotypes. Comparison with a referent group (blood donors)

demonstrated that a significantly lower proportion of patients fell into the Apo-E 2/2 and 2/3 groups, whereas a significantly higher proportion of patients fell into the Apo-E 4/4 group. However, the overall proportion of patients with these genotypes was very low: those with the Apo-E 2/2 genotype comprised only 0.25%; those with the Apo-E 2/3 comprised 9.5%; and those with Apo-E 4/4 comprised only 3.5%, making interpretation of these observations difficult. Pre-challenge urinary mercury concentrations were ~5 ug/g creatinine [6.5 µg/L]; post-challenge concentrations were 347 µg/g creatinine [451 µg/L]. Sources of mercury were not reported/known. There was no attempt to correlate post-chelation urinary mercury concentrations and Apo-E genotypes.

Høl et al. (2001) investigated selenium concentrations in persons who had been examined with respect to general health problems associated with dental amalgam fillings. Healthy controls (n=21) with amalgam fillings and patients who claimed symptoms from existing amalgam fillings (n=20) were assessed. The median concentration of selenium in blood was significantly lower in subjects who claimed symptoms of mercury amalgam illness (119.2 µg/L) than in healthy subjects with amalgam (130.3 µg/L); the difference was more evident in individuals with more than 35 amalgam surfaces. The authors note that a cause-and-effect relationship between the presence of dental amalgam and reduced selenium concentrations cannot be established, but speculate that persons with ill-health attributed to dental amalgam exhibit impaired selenium metabolism compared to healthy people.

Rose et al. (2008) looked at the frequency of two enzyme polymorphisms in 450 children with autism and 251 unaffected controls. The two enzymes studied, δ-aminolevulinic acid dehydratase (ALAD) and coproporphyrin oxidase (CPOX), are inhibited by low concentrations of lead and mercury, respectively. The hypothesis was that autistic children would have increased concentrations of polymorphisms in these two enzymes that are part of the heme biosynthetic pathway and therefore be more susceptible to the adverse effects of low concentrations of lead and/or mercury. Heme is a vital component of several key proteins such as hemoglobin, the metabolic enzyme cytochrome p450 family, mitochondrial respiratory cytochromes, and nitric oxide synthase which catalyzes the synthesis of nitric oxide, a signal transduction molecule. Interference with enzymatic steps in heme biosynthesis can result in increased excretion of porphyrins, heme precursor molecules, in the urine. At least one earlier study reported higher urinary porphyrin excretion in autistic children. The authors found a significant increase in an ALAD variant in 242 of the autistic children which was associated with decreases in plasma glutathione (a multi-function molecule which can also detoxify metals) and in the reduced/oxidized glutathione ratio. Contrary to the initial hypothesis, the frequency of CPOX variants was significantly decreased in autistic children. This CPOX result led the authors to suggest that mercury-related porphyrinuria, if observed in autistic children, is likely related to metal exposure that is independent of the CPOX variant alleles. Thus, the authors concluded that children with autism who inherit a specific ALAD allele and have lower glutathione concentrations may be at increased risk for lead toxicity during development.

Summary of reports on human susceptible/sensitive populations

Results from the prospective, randomized, New England Children's Amalgam Trial on renal function in children did not support an effect of low-level mercury exposure from dental amalgam on excretion of urinary nephrotoxicity biomarkers (see review in the 2006 White Paper). Specific polymorphisms for enzymes that decrease GSH availability were reported to effect a decreased metabolism of inorganic mercury resulting in increased tissue and urinary concentrations, theoretically rendering individuals with such polymorphisms more susceptible to mercury toxicity. However, no health outcomes were reported. Likewise, Apo-E genotyping has been investigated as a possible indicator of susceptibility to heavy metal neurotoxicity but data to date are inconclusive. In subjects who reportedly suffered from 'mercury amalgam illness', concentrations of selenium in blood were significantly lower than in healthy subjects with amalgam and the difference was more evident in individuals with a large number of amalgam surfaces but no cause and effect relationship could be established. Other investigators studying the frequency of CPOX variants in autistic children found that, in contrast to their initial hypothesis, the variant frequency was significantly lower in autistic children, suggesting that polymorphisms in this allele are not likely contributing factors in autism. Considered together, the reports reviewed in this section provide little support to suggest the children nor individuals with particular genetic polymorphisms are more sensitive to mercury than the general population, but in some cases, may warrant further investigation.

Human Cardiovascular System (1)

Frisk et al. (2006) determined the plasma and erythrocyte concentrations of a number of trace elements before and after removal of dental amalgam and other metal alloys. The study is difficult to interpret since the number and type of dental restorations removed was not quantified, nor was the time after removal during which the trace element analyses were conducted. In addition, all subjects were treated with a variety of vitamins and anti-oxidants before the analyses were done, serving to confound the interpretation of the data. One relevant finding was that the plasma and erythrocyte concentrations of copper, selenium and mercury all decreased after removal of dental restorations and anti-oxidant/vitamin treatment.

Summary of human cardiovascular report

Removal of dental restorations led to a decrease in the plasma and erythrocyte concentrations of copper, selenium and mercury.

Human Cancer (3)

Boffetta et al. (1998) evaluated the incidence of cancer in over 7000 persons from four mercury mines and mills in Europe. Exposures to mercury vapor and dust were very high over long periods of time. This body of work contributes additional evidence that chronic occupational exposure to inorganic mercury in mines and mills is not associated with cancer risk, with the possible exception of liver cancer [standardized mortality ratio of 1.64]. There was, however, no trend in the incidence data for any cancers and duration of exposure.

Hougeir et al. (2006) present pilot data on the role of oral metal contact allergy in the development of oral squamous cell carcinoma (SCC). The authors describe results with 11 patients (aged 34–81) with SCC and metal restorations who underwent patch-testing with a metal series. The mean number of years for all patients with metal dental restorations was 21 years for gold restorations and 32 years for amalgam restorations. Most of the patients with relevant patch test results had a relatively low or distant exposure to traditional risk factors for oral SCC (tobacco, alcohol). The prevalence of positive patch test reactions to gold, mercury, silver, and copper was higher in the study population than reported in the general population. Intraoral cancer has not been reported to develop in patients who are allergic to other agents, perhaps because these agents generally are in contact with the oral mucosa relatively briefly. Three of four relevant subjects in the study who had their metal dental restorations removed noted improvement of their oral signs and symptoms in a 2- to 3-year follow-up period. The authors recommend patch-testing for dental metals for patients with atypical lesion or lichen planus-like lesion near a metal restoration.

Navas-Acien et al. (2002), in a retrospective review of a very large Swedish population database (n = 33,359,168) linking cancer diagnoses to occupational and demographic data obtained in a 1970 census, estimated relative cancer risk after adjustment for age, period, geographical area, and town size. The main findings of the study were an increased risk of glioma with occupational exposure to arsenic, mercury, and petroleum products. No specifics on type or amount of mercury exposure were reported.

Summary of reports of human cancer

The reports summarized in this section do not provide evidence that mercury exposure via either dental amalgam or occupational exposure in mines or mills is related to increased cancer incidence with the possible exception of liver cancer and glioma after occupational exposures. The specifics on the type, duration and/or amount of mercury exposures were not reported.

Animal Developmental Disposition and Toxicity (5)

Aschner et al. (1997) exposed pregnant rats to mercury vapor (300 μg/m^3, 4 hr/day) on gestational days 7 to 21, and determined that fetal brain metallothionein (MT) mRNA concentrations were significantly higher than controls at term (gestational day 21). In general, metallothioneins represent intracellular proteins with a variety of functions, such as metal homeostasis and cellular defense generally via high-affinity metal sequestration. In addition, astrocytes from exposed and control animals were isolated and cultured *in vitro* for up to three weeks. Cultures of cells exposed to mercury *in utero* expressed significantly more MT mRNA and MT proteins than controls. No evidence for glial or neuronal cell damage was presented in this study. These data suggest that MT markers are useful indicators of intrauterine exposure to mercury vapor and that MT induction in fetal astrocytes may represent an attempt by glial cells to protect glia, and perhaps other cell types such as neurons, against mercury cytotoxicity.

Fredriksson et al. (1996), exposed pregnant rats to very high doses of either methylmercury (2 mg/kg/day during gestational days 6 to 9) and/or mercury vapor (1.8 mg/m^3, 1.5 hours/day during gestational days 14 to 19). Clinical observations and developmental markers out to weaning showed no treatment-related effects. At 4 to 5 months of age, animals underwent behavioral assessments in spontaneous motor activity and water and radial arm mazes. Results showed that prenatal exposure to mercury vapor caused alterations in both spontaneous and learned behaviors in animals as adults and that co-exposure to methylmercury (which alone did not significantly affect these measures) significantly aggravated these changes.

Morgan et al. (2006) exposed pregnant rats to high concentrations of mercury vapor (1, 2 or 4 mg /m^3) or air (controls) during pregnancy, and total mercury concentrations were determined in neonatal brain, liver and kidney at various times after birth out to 90 days of age. Milk was analyzed between birth and weaning. Before weaning, mercury concentrations in neonatal tissues were proportional to maternal exposures and were highest in kidney followed by liver > brain. There was no apparent elimination of mercury prior to weaning. After weaning, a much greater increase in neonatal mercury accumulation occurred as animals began to eat a diet containing trace concentrations of methylmercury, a fact unknown until after the study was started. Dietary exposure to trace amounts of methylmercury can result in a significantly greater accumulation of mercury in neonates than gestational exposure to high concentrations of mercury vapor.

Orct et al. (2006) administered both organic (thimerosal, ethylmercury) and inorganic mercury (mercuric chloride) to suckling rats on postnatal days 7, 9 and 11, and tissue concentrations of organic and inorganic mercury were determined on postnatal day 14. In animals receiving organic mercury, tissue concentrations of total mercury were highest in blood and brain, whereas for animals receiving inorganic mercury, tissue concentrations of total mercury were highest in liver and kidney. These data indicate distinct differences in tissue distribution for the various forms of mercury.

Takahashi et al. (2001) analyzed the distribution of mercury released from a single dental amalgam (3.8 to 5.5 mg total weight) placed in pregnant rats on day 2 of pregnancy in both maternal and fetal tissues. The amount of mercury released increased 7-20 fold after chewing. The highest concentration of mercury in fetal organs was found in liver, followed by kidneys and then brain. Mercury concentrations in fetal brain were not different from controls, but concentrations in maternal organs and fetal liver were significantly higher than controls. These data demonstrate fetal exposure from maternal exposure to dental amalgam.

Summary of reports on animal developmental disposition and toxicity

All studies evaluated in this section were conducted in rats and results from several confirm earlier data that fetuses are exposed to maternal sources of elemental mercury vapor and mercury distributes throughout the body including brain. Fetal brains exposed to high doses of Hg vapor *in utero*, had significantly higher metallothionein (MT) mRNA concentrations, suggesting that MT induction may represent a cellular defense mechanism to protect against mercury exposure. Prenatal exposure to high concentrations of mercury vapor caused

alterations in both spontaneous and learned behaviors in offspring as adults, and co-exposure to methylmercury significantly aggravated these changes. In neonates from dams exposed to high concentrations of mercury vapor during gestation, mercury tissue concentrations before weaning were proportional to maternal exposures. Dietary exposure to trace amounts of methylmercury after weaning resulted in a significantly greater accumulation of mercury in neonates than gestational exposure to high concentrations of mercury vapor; this observation suggests a clear need to know the concentrations of mercury in feed. The amount of mercury released increased from dental amalgam in pregnant rats after chewing increased 7-20 fold. Fetal brain mercury concentrations were not different from controls. Clear differences in tissue distribution for the various forms of mercury were observed in suckling rats given both organic and inorganic mercury; tissue concentrations of total mercury were highest in blood and brain for animals given organic mercury, but were highest in liver and kidney in animals given inorganic mercury.

Animal Immune System/Susceptible Populations (3)

Abedi-Valugerdi et al. (2001) found that the resistance to mercury was a dominant trait in a mouse model of genetic resistance to mercury-induced immunoglobulin (Ig) G1 antibody formation, IgE synthesis, renal IgG deposits and antinucleolar autoantibodies production. In addition, they also suggest that genes at a specific locus (the H-2 loci) strictly contribute to the inheritance of resistance to mercury -induced antinucleolar autoantibody production and that non-H-2 genes mainly govern the inheritance of unresponsiveness regarding other characteristics. These data indicate possible mechanisms of gene-mediated susceptibility/resistance to mercury.

Hultman et al. (1998) showed that in the genetically mercury-sensitive Brown-Norway rat, placement of mercury amalgams in four molars of the upper jaw was sufficient to give rise to activation of the immune system and system immune complex deposits. Mercury-resistant Long-Evans rats treated similarly did not show any such reactions. Tissue concentrations of mercury were reported for the Brown-Norway rats with concentrations being greatest in kidney > spleen > brain >liver > thymus. These data again demonstrate genetic susceptibility to mercury-induced immune responses and that mercury from amalgam distributes to tissues.

Johansson et al. (1998) provides data showing that genotype determines the B cell response to mercury in mice. Subcutaneous mercuric chloride was used to elicit the response which also illustrated the importance of non-H-2 genes for regulating the response to mercury.

Summary of reports on animal immune system/susceptible populations

Two mouse studies and one rat study indicate that genotype plays a role in immune system responses to mercury and the rat study indicated that placement of mercury amalgam in the molars of rats was sufficient to give rise to systemic activation of the immune system.

Animal Nervous System (3)

Pendergrass et al. (1997) studied the effects of inhalation of mercury vapor (250 or 300 ug/m^3, 4 hours/day for up to 28 days; whole body exposure) in rats. Brain mercury concentrations increased with exposure duration and after 14 days, there were significant reductions in photoaffinity labeling of the beta-subunit of tubulin dimers by radiolabeled GTP. The authors suggest this neurochemical lesion is identical to that observed in 9 of 12 Alzheimer's disease (AD) brains similarly examined. In the human brains, however, there were no significant differences in mercury concentrations between AD and controls, making interpretation of these findings difficult.

Stankovic (2006) studied the acute exposure of young adult mice to mercury vapor concentrations of 500 μg/m^3 for 4 hours (whole body exposure, n = 6 treated and 6 control mice) followed by assessment of forelimb grip strength at 4 week intervals until sacrifice 7 months after exposure. At the end of the study, the morphology of myelinated motor axons was assessed. The author suggests that mercury vapor significantly reduces axon diameter (no change in number); however, the mean differences were very small and there were large overlaps in the variability measures, rendering the data unconvincing. Forelimb grip strength appeared to wane more rapidly in mercury-exposed mice as they aged, and granular deposits, presumed to be mercury but never confirmed, were reported in the cytoplasm of the spinal cord ventral horn motor neurons.

Yasutake et al. (2003), in studies of very high mercury vapor exposure (8.3 mg/m^3, 15 hour total over 5 days, whole body exposure) in young adult rats, reported, as expected, high brain (cerebrum and cerebellum) mercury concentrations of ~5 to 10 μg/g tissue. Concentrations of total metallothionein were increased 2- and 3-fold in cerebrum and cerebellum, respectively, and remained elevated for at least 3 weeks after exposure cessation.

Summary of reports on animal nervous system

All studies employed whole body exposures of mice or rats to mercury vapor and brain mercury concentrations increased with duration of exposure. Whole body exposures are problematic since mercury deposition on fur can result in ingestion upon subsequent grooming. After 14 days of exposure, there were significant alterations in tubulin binding characteristics that were reported to mirror those observed by the same group in some Alzheimer's brains similarly examined; however, there were no significant differences in mercury concentrations between AD and control brains, making interpretation of these findings difficult and the correlation of the observations problematic. In young adult rats, high mercury brain concentrations were reported after whole body exposure to very high concentrations of mercury vapor and brain levels of metallothionein were increased. In young adult mice similarly treated, axon diameter was significantly reduced but the data were unconvincing; forelimb grip strength waned more rapidly in mercury-exposed mice as they aged.

Antibiotic Resistance (3)

Pike et al. (2002) sought to determine if the prevalence of mercury-resistant oral bacteria was greater in children with mercury amalgam fillings than in those without amalgams. A secondary goal was to determine if the mercury-resistant isolates were also antibiotic resistant. Bacteria in the dental plaque and saliva from 41 children with amalgams and 42 children without amalgams were screened for mercury resistance by cultivation on $HgCl_2$-containing medium. There was no significant difference in the prevalence or proportion of mercury-resistant bacteria in children with amalgam fillings and those without amalgams. The authors point out that there are few studies suitable for direct comparison, and there are many methodological differences between studies. They note there is no internationally accepted criterion for "mercury resistance" and that a variety of $HgCl_2$ concentrations are used in test media to differentiate between sensitive and resistant strains of bacteria.

Pike et al. (2003), in a subsequent study, looked at whether placement of mercury amalgam in children's teeth induces an increase in oral bacteria resistant to mercury, penicillin, ampicillin, erythromycin, or tetracycline. Dental plaque and saliva samples from 16 children without mercury amalgams were screened for bacteria resistant to mercury or to one of the antibiotics prior to, and one month after, placement of amalgam. Following amalgam placement, there was no significant increase in the number of children harboring bacteria resistant to the antibiotics mentioned, and there was no increase in the proportions of such organisms. The authors conclude the presence of mercury fillings in children's teeth has little effect on the prevalence of mercury- or antibiotic-resistant oral bacteria.

Wireman et al. (1997) report on mercury resistance and antibiotic resistance in fecal bacteria of primates. Fecal bacteria from three longitudinal mercury exposure experiments in monkeys (n =2/study) and from two independent survey collections were examined for their carriage of the mercury resistance (*mer*) locus. In the monkey studies, bacterial isolates were obtained before mercury amalgam placement, during the 5 to 10 weeks that amalgam was in place, and after amalgam removal. The two survey collections of bacteria were the ECOR collection, a standard reference collection used in E. coli population biology studies, and the Environmental Plasmid Survey (EPS) collection which consists of fecal strains isolated from humans in the late 1970s. The occurrence of antibiotic resistance was assessed in both mercury-resistant (Hg^r) and mercury-susceptible (Hg^s) strains. Hg^r strains of bacteria were recovered from monkeys prior to installation of amalgam dental restorations and frequently these strains became the dominant strains while amalgams were installed. These persistent Hg^r strains always carried the same *mer* locus throughout the experiments. In general, strains with any mer locus were more likely to be multiresistant than were strains without mer loci. The majority of highly multiresistant Hg^r strains also carried genes characteristic of an integron, a novel genetic element which enables the formation of tandem arrays of antibiotic resistance genes. Hg^r strains lacking antibiotic resistance show no evidence of integron components.

Summary of reports on antibiotic resistance

Two studies in children concluded there is no link between mercury amalgam fillings and the prevalence of mercury-resistant or antibiotic-resistant oral bacteria. Since there is no

internationally accepted criterion for “mercury resistance”, and a variety of $HgCl_2$ concentrations are used in media to differentiate between sensitive and resistant strains of bacteria, comparisons across different studies are difficult. Mercury-resistant strains of fecal bacteria were recovered from monkeys prior to installation of amalgam dental restorations and frequently these strains became the dominant strains while amalgams were installed. The majority of highly multi-resistant, mercury-resistant strains from the monkey studies and other bacterial repositories also carried genes characteristic of an increased ability to develop antibiotic resistance. In light of the findings from the studies in children, the significance of the monkey studies is not known.

V. Review of Case Studies Related to Health Effects Attributed to Dental Amalgam Mercury (unless otherwise specified, the terms 'Hg' and 'mercury' refer to total mercury measured and include both organic and inorganic forms)

Summaries of 33 case studies related to the effects of mercury vapor from a variety of sources, including effects attributed primarily to dental amalgam, but also responses after exposure to mercury in other scenarios, such as occupational, manipulating elemental mercury, or suicide attempts, are presented here. For purposes of this Addendum to the 2006 FDA White Paper, case studies are generally defined as reports consisting of information from one to approximately 10 individuals, and generally do not include control subjects. Of the 33 case studies identified from the literature database search, 15 studies focus on effects on skin and mucous membranes; 5 studies focus on effects on the nervous system; 3 relate to effects on the pulmonary system; 1 to effects on the musculoskeletal system; and 1 to effects on the gastrointestinal system. Five of the case studies involve mercury poisoning from various sources, and 3 discuss the effects of chelating agents for removal of mercury.

Case Studies: Effects of Mercury on Skin and Mucous Membranes (15)

Fifteen case studies present findings on the effects of mercury on the skin and mucous membranes, one of which includes psychiatric effects and one which mentions zinc as another potential allergen contained in dental amalgam.

Adachi et al. (2000) reported two case studies and suggest that oral ingestion and direct contact with metal allergens may play a role in provoking or aggravating nummular dermatitis in certain patients. A 32-year-old male dentist had multiple exudative erythematous plaques accompanied by severe itching on his extremities and trunk for three years. Two weeks after having his dental amalgams removed, his skin symptoms improved dramatically, recurring only with contact with a patient's amalgam. Subsequent strict avoidance of contact with amalgam improved his condition. A 70-year-old male desk worker had several months' history of multiple nummular exudative eczematous plaques on his legs and trunk. Following a reaction to a patch test, it was recommended he have his dental amalgam removed. One month after amalgam removal, his eruption subsided absolutely, leaving pigmentation.

Al-Mutair et al. (2004) report the case of a 48-year-old man with histologically proven lichen planus involving the left half of his lower face, which had previously been affected by herpes zoster. His history revealed he had dental amalgam fillings 2 months before the appearance of the lesions on the same side of his face, although the oral mucosa in contact with the fillings was normal. The dental amalgam was removed, and the lesions resolved within 6 weeks, leaving residual pigmentation. The authors suspect the dental amalgam triggered an isotopic response at the healed herpes zoster sites, and the mechanism for this phenomenon is unknown.

Bleiker & English (1998) report the case of a 19-year-old woman who presented feeling generally unwell and with severe gingivostomatitis, intraoral ulcers, and cervical lymphadenopathy 2–3 days after insertion of a large amalgam filling. The filling was removed, and the symptoms disappeared with no further problems. The authors remind that acute contact allergy to mercury in dental fillings does occur, and that there are many other sources of mercury exposure.

Camisa et al. (1999) provide three case studies suggesting oral lichenoid lesions caused by hypersensitivity to mercury in amalgam fillings may mimic oral lichen planus (OLP). They note the onset of OLP is typically in middle-aged persons, the majority of whom have metallic dental restorations or constructions. Patients in the case studies ranged in age from 50 to 57. The authors suggest lichenoid stomatitis was probably caused by contact hypersensitivity to mercury in adjacent amalgam fillings, based on clinical appearance, positive patch test results, and response to complete amalgam removal. They recommend that patients with oral lichenoid lesions in apposition to amalgam fillings have allergy patch testing with relevant materials. If positive patch results are obtained in symptomatic patients, removal and replacement of amalgam fillings with other materials can be justified.

Kato et al. (2003) report a patient with lichen planus of the buccal mucosa, the nails, and the skin caused by mercury allergen. Patch-testing showed positive reactions to the toothpaste he used, sodium *N*-lauroyl sarcosinate 0.5% aq., mercury 0.05% pet., ammoniated mercuric chloride 1.0% pet., and thimersol 0.1% pet. When his mercury-containing dental fillings were replaced, the mucosal and nail symptoms gradually improved.

Fardal et al. (2005) present a case study indicating that release of mercury from amalgam fillings induces hypersensitivity reactions resulting in soft-tissue changes in the gingival, buccal mucosa, and tongue surfaces, and on the skin on the back of the hands. The case study involved a 73-year-old man who developed mucosal changes deemed to be related to his old, corroded amalgam fillings. The amalgams on the left side of his mouth were replaced, and his condition improved to close to normal. However, 4–6 weeks later, he developed lesions on his hands. Patch-testing revealed an allergic reaction to mercury, and the fillings on the right side of his mouth were replaced or covered with crowns. Both his skin and the oral mucosa returned to normal, and in the following 4 years, no further lesions were observed. The authors point out that amalgam removal can also result in improvements in patients with negative patch (allergic) results.

Guttman-Yassky et al. (2003) present a case study of a 63-year-old woman who had orofacial granulomatosis (OFG) as part of a delayed hypersensitivity reaction, most likely resulting from amalgam fillings, as indicated by positive patch testing for mercury. She experienced complete resolution of her symptoms following removal of all amalgam. The authors propose that mercury in amalgam fillings is one cause of OFG and suggested this is identifiable with appropriate patch-testing.

Lazarov et al. (2003) provide two case studies describing patients with OFG induced by contact to gold and possibly mercury. A 65-year-old woman presented with erythema of her upper lip that had lasted 10 months. She had gold crowns on her upper incisors placed 5 years earlier. After patch-testing, she was advised to have the gold dental crowns replaced. There was marked improvement 3 months after the replacement, and total involution of OFG after 5 months. Three years later, she was still healthy. A 32-year-old woman presented with longstanding edema and erythyma of her lower lip that had appeared after the start of replacement of several, old, eroded amalgam fillings. After patch-testing, she was advised to have her mercury amalgams completely replaced, but she was unwilling to undergo the treatment. Two years later, the lip and tongue swelling had increased. The authors postulate that the OFG in their patients was the result of an allergic contact reaction to gold and mercury. Alternatively, it could be speculated that OFG was an expression of a granulomatous contact allergic reaction provoked by the metals.

Matsuzaka et al. (2006) describe a 55-year-old woman with gingival pigmentation in the maxillary incisor area. Earlier, in 1977, she had amalgam-like metal removed that had remained after a procedure in 1964. Because of this and additional signs and symptoms, she had patch-testing and reacted positively for tin, indium, and zinc. An extirpation operation removed granulation tissue with foreign bodies, and all dental materials were removed. Ten months later, all symptoms had improved. The authors suggest that metals remaining inside the body, such as dental implants and sealing materials for reverse root-ends or perforations evoke symptoms in patients with metal allergies, rather than crown material itself.

McGivern et al. (2000) present case studies of two individuals with hypersensitivity reactions possibly attributable to substances in the dental office environment. A 50-year-old man had soreness and lesions on the buccal mucosa and tongue, in close proximity to amalgam restorations. After patch-testing, the patient's dentist made restorations that either covered or replaced the amalgam. Within 2 months, the patient was asymptomatic, and at 12 months follow-up, the lichenoid lesions had completely resolved. A 57-year-old woman was referred for a history of developing intraoral blistering and facial rash soon after dental treatments. After patch-testing was positive for mercury, the patient and her dental and medical practitioners were advised that alternative restorative materials should be used and that removal of amalgam in the future should be done with use of a rubber dam and high-speed suction to reduce exposure to free mercury that might be released. The authors suggest the most common type of hypersensitivity to amalgam is delayed oral lichenoid reaction (OLR), with the allergen most often being mercury. Some patients can have amalgam restorations without effect for years but later become sensitized, then consistently react with lesions. Localized reactions commonly result in rashes, and if more severe, edema, tachycardia, and respiratory difficulty can occur.

Nakamura et al. (1999) present a case study of a 22-year-old woman with a draining sinus tract on one cheek. The tooth responsible was restored with amalgam filling, and radiographic examination revealed base or pulp capping material below the restoration and a radiolucent periapical lesion surrounding the distal root apex. Conservative, nonsurgical root canal

treatment was performed, and 10 months later the sinus had healed completely, and the periapical lesion had resolved. The tissue recovered during treatment revealed foreign bodies, including amalgam, associated with inflammation. The findings suggest chronic inflammation in the pulp tissue had resulted from capping material and amalgam left behind 10 years previously that had acted as an antigen causing the reaction resulting in the draining sinus tract.

Pigatto et al. (2002) present a case study involving a 36-year-old woman with an itchy lichenoid patch of dermatitis on her cheek. She reported depression, malaise, difficulty concentrating, and poor memory. The patient was patch-tested and found to be positive to amalgam. She had 34 dental amalgam surfaces, and the total mercury in her saliva was 1.40 µg/L. Dental restorations with ceromer replacement fillings took place over a period of 5 months, but she began to improve after 4 months. At 5 months, her saliva mercury concentration was reduced 40% to 1 µg/L. Her nummular lichenoid dermatitis and her neuropsychologic symptoms disappeared after total amalgam replacement.

Pigatto et al. (2004) report the case of a 65-year-old woman with burning mouth syndrome (BMS) associated with a strong allergic reaction to mercury and with systemic contact dermatitis that started a few months after a dental amalgam restoration. The woman also had symptoms of xerostomia (dry mouth), a metallic taste in her mouth, and other skin lesions. The patient was patch-tested and demonstrated strong positive reactions to mercury. During testing, her symptoms worsened. The new amalgam filling was in contact with a gold crown, and oral galvanism was detected. Mercury concentration in saliva was below the detection limit (0.1µg/L). A diagnosis was made of BMS type 3 resulting from allergy to mercury in amalgam, with the recommendation for total replacement of her single amalgam filling. Without any medical treatment, she achieved complete remission of her oral complaints 10 days after removal of the dental amalgam. The systemic dermatitis settled with a few weeks. Twenty-four months later, there was no evidence of recurrence of either the oral or systemic disorders. The authors suggest the role of allergy in this case and that mercury exposure resulting in saliva mercury concentrations below detection limit may adversely affect the immune system in individuals with high susceptibility.

Segura-Egea & Bullon-Fernandez (2004) present a case study of a 38-year-old woman with oral lichenoid reaction (OLR) lesions related to contact with an amalgam restoration, suggesting hypersensitivity to mercury. She was not aware of the lesion noticed by the dentist, though she had noticed some sensitivity, and she decided not to have the filling replaced. Other restorations were performed with composite resins, and no reactions occurred. The authors report that in 95% of patients with OLR lesions in direct contact with amalgam, the lesions disappear after removing the amalgam. They recommend safety precautions (rubber dam, high-volume suction, abundant irrigation) when removing amalgam.

Wohrl et al. (2001) present a case study showing that rarely zinc, as a component of dental amalgam, is the cause of sensitization, rather than mercury.

Summary of Case Studies Related to Effects of Mercury on Skin and Mucous Membranes

Together, the case studies above suggest various types of lesions of the skin, mouth, and tongue might sometimes occur as a result of mercury-containing amalgam. The skin conditions include nummular dermatitis, oral lichenoid planus, gingivostomatits, ulcers, various mucosal changes, burning mouth syndrome, orofacial granulomatosis, erythema, swelling, itching, and pigmentation. In some cases, the conditions are the result of direct contact with the amalgam filling, and in other cases, signs and symptoms develop without direct contact. In some cases, the skin conditions appear on the hands and other parts of the body rather than only within or around the mouth and face. Two cases refer to amalgam material left behind after a procedure that became a chronic irritant, apparently inducing signs and symptoms. Some authors suggest hypersensitivity or allergy to mercury, often indicated by patch-testing, as the likely cause of the dermatologic reactions. It is notable that in all the case studies where amalgam was removed, there was prompt resolution of signs and symptoms. Though focused on dermatological effects, one of the studies (Pigatto et al., 2002) also observed relief from self-reported depression, malaise, difficulty concentrating, and poor memory in a patient after amalgam removal. In a case presented by Yoshida et al. (1999) in the section below on effects of mercury on the pulmonary system, the authors suggest that with respect to skin patch-testing, there may be differences in allergic reactions between the skin and the lungs.

Case Studies: Effects of Mercury on the Nervous System (5)

Five case studies present findings on the effects of mercury on the nervous system, with symptoms including tremors and parasthesia, changes in hearing and visual evoked responses (VER), and peripheral neuropathy. Two of the reports involve occupational exposure and 3 involve exposures attributable to dental amalgam.

Donoghue at al. (1999) present a case study of a 19-year-old man who developed tremor in both hands and fatigue after starting work at a Placer gold mine where he was exposed to elemental mercury used to amalgamate gold. Examination revealed an intention tremor, dysdiadochokinesis (inability to perform rapid, alternating movements), and mild rigidity. The man worked 60 hours per week in a small room without windows and with poor ventilation. He used a face respirator for some activities, but not others. Food was eaten in the room, there was poor hygiene, and there was no showering or changing before leaving work. Peak air concentration of mercury vapor was 0.533 mg/m^3 (the ACGIH 2001 mercury vapor Threshold Limit Value is 0.025 mg/m^3). Urine collected for 24 hours indicated a mercury concentration of 715 nmol/L (143 µg/L). After removal from working in the gold processing room, his tremor had almost resolved by 7 weeks later, the dysdiadochokinesis and rigidity was no longer evident, and his 24-hour urinary mercury concentration had fallen to 160 nmol/L (32 µg/L). [For comparison, the subjects in the study (Fawer et al., 1983) used to derive the 1999 ATSDR Minimal Risk Level (MRL) had an average urinary mercury concentration of 26.1 µg/L; increased hand tremor velocity was associated with this urinary mercury concentration]. In the 2006 FDA White Paper, five studies confirmed that, in the general population that is not occupationally exposed to mercury, average urinary mercury concentrations are in the range of 1-3 µg/g Cr (1.3-3.9 µg/L) (Factor-Litvak et al., 2003; Bellinger et al., 2006; DeRouen et al., 2006; Kingman et

al., 1998; Dye et al., 2005); no neurological or kidney function deficits were noted in these subjects when evaluated as part of the study.]

Hsu et al. (1999) present the case study of a 48-year-old Chinese steelworker who cut steel plates with an oxyacetylene torch. It was later determined the ship had once stored oil rich in elemental mercury, and the steel plates contained a very high mercury level. That evening the man developed dyspnea, which worsened in the night, associated with mild left-sided chest discomfort. He sought medical attention 24 hours after the exposure and was diagnosed with chemical pneumonitis secondary to fume inhalation. He improved with intravenous cortisone and antibiotics. The patient's urinary mercury concentrations were found to be grossly elevated at 248.8 μg/L [192 μg/g creatinine], confirming a diagnosis of mercury poisoning. The patient recovered well without chelation, and at discharge 18 days later, his urinary mercury concentration was 63.3 μg/L [49 μg/g creatinine]. Neurobehavioral testing performed a month after the incident showed poor scores for motor speed and steadiness, compared to the reference group. He also complained of irritability, restlessness, depression, and numbness of fingers. Nerve conduction studies suggested some degree of peripheral neuropathy. At 3-month follow-up, he had no further irritability or restlessness, but there was no significant improvement in nerve conduction. Screening other workers who had carried out similar work revealed another seven workers with very high urinary mercury concentrations (three exceeded 100 μg/L).

Hilu & Zmener (1999) present a case study of a 15-year-old boy who developed mental nerve (a general sensory nerve in chin, lower face and lip) paresthesia associated with an amalgam filling placed in direct contact with the pulp of a mandibular first molar. Three days after the amalgam placement, the molar was painful and the patient developed a persistent extraoral numb sensation in the lower left lip and chin. He was prescribed antibiotics and analgesics with no other treatment. Two months after having the filling placed, the boy reported severe pain along with the parasthesia. Given a diagnosis of irreversible pulpitis, endodontic therapy was completed in two visits. When the amalgam filling was removed, it was found to be in direct contact with the dental pulp. Two days after the initial visit, the patient reported the tooth had remained comfortable, the numbness had disappeared, and the soft tissues felt normal again. Two weeks after the treatment was completed, the tooth remained comfortable, and the patient was referred to his general dentist for definitive restoration of the crown. At 6 months, the patient was free of all symptoms. Epicutaneous patch tests for response to the metals in dental amalgam including mercury proved positive for the reagents tested.

Siblerud & Kienholz (1997a) evaluated 7 female subjects (aged 32–46) with amalgam fillings and diagnosed with multiple sclerosis (MS) who were tested for hearing loss at threshold frequencies of 250, 500, 1000, 4000, and 8000 Hz. The subjects then had their amalgam fillings removed and replaced. Between 6 and 8 months after amalgam removal, testing for hearing was repeated, with an average improvement of 8 dB ($p = 0.02$). The authors refer to a 1971-72 outbreak of methylmercury poisoning in Iraq where hundreds of people were poisoned; severely affected children became deaf, and many adults developed marked hearing loss. The

authors further suggest that amalgam mercury may be involved in hearing loss of MS patients and could be an etiological factor in the hearing loss of non-MS patients.

In another case study, Siblerud & Kienholz (1997b) performed visual evoked response (VER) tests on seven female subjects (aged 32–46) with amalgam fillings and diagnosed with multiple sclerosis (MS). About 6 months after the subjects had their amalgam fillings removed, a second VER test was performed on all subjects, and the latencies of the VER decreased significantly. The mean latency of P1 for the right and left eye combined decreased by 23.1 milliseconds ($p=0.011$), and N1 of the right and left eye combined decreased by 31.7 milliseconds ($p=0.026$). The authors reference studies where mercury concentrations of cerebral spinal fluid of MS patients were found to be eight times higher than non-MS patients. The authors note that mercury also has the ability to cause autoimmune reactions, a leading theory on the etiology of MS. They point to clinical evidence that mercury slows down nerve conduction velocity and suggest that the findings here are consistent with the hypothesis that mercury from dental amalgam may be associated with multiple sclerosis.

Summary of Case Studies Related to Effects of Mercury on the Nervous System

In one occupational-related case, exposure to high levels of mercury vapor in a gold mine resulted in an intention tremor, dysdiadochokinesis, and mild rigidity. Health improvement was observed when the subject was removed from the source. In a second occupational case, a steelworker was exposed to mercury and developed irritability, restlessness, depression, numbness of fingers, and peripheral neuropathy. After removal from the source, the urinary mercury concentration decreased markedly (still higher than concentrations reported in persons with amalgam restorations); but neurological symptoms did not improve. In a case where dental amalgam was in contact with dental pulp, one subject developed parasthesia and pain, which were relieved by removal of the amalgam. In two cases involving women with amalgam fillings and diagnosed with multiple sclerosis, improvement in both hearing and VER with removal of amalgam was reported. The authors of the two multiple sclerosis case studies (Sibelrud & Kienholz) speculate that mercury from dental amalgam may be associated with development of multiple sclerosis. In most cases, conclusions beyond the particular case are difficult to interpret due to the lack of appropriate control groups (a short-coming of almost all case studies) such as individuals without MS who have amalgam restorations.

Case Studies: Effects of Mercury on the Pulmonary System (3)

Three case studies focus on the effects of mercury on the pulmonary system. One case represents deliberate exposure to liquid mercury and mercury vapor, one from occupational exposure, and one attributed to dental amalgam.

Glezos et al. (2006) provide a case study of a 43-year-old man who presented with a 6-day history of cough, pyrexia, rigors, pharyngitis, nausea, back and epigastric pain, and a maculopapular rash. Three months earlier he had been assessed for gambling addiction and suicidal ideation. He was treated with antibiotics and discharged in improved condition. About one week later, he admitted to his doctor he had ingested a “few sips” of liquid mercury a week

before the onset of his illness and that he had also heated mercury and inhaled the vapors on at least three occasions over a period of 2–3 days. Within 2–3 hours of inhalation, he became polydypsic with reduction in urine output and observed mercury in his stools. His 24-hour urine collected approximately 5 weeks after the event measured 970 nmol/L mercury (normal range less than 250 nmol/L). After two courses of chelation over a 6-week period, his urinary mercury normalized to 29 nmol/L, and no further treatment was provided. The authors note that although there was spontaneous improvement of pneumonitis, chelation therapy was indicated in an attempt to prevent sequelae associated with mercury poisoning.

Hashimoto et al. (2001) present a case study of eight men aged 37–54 (all smokers) exposed to mercury vapor during an accident when cutting pipes in a sulphuric acid plant in 1997. All the workers were wearing masks to prevent inhalation of sulphur dioxide. Four complained of shortness of breath, dry cough, and generalized weakness during the cutting process. One of the four continued to have symptoms and visited the emergency room the next day. The other three individuals improved slowly, but pulmonary symptoms remained, and eczema developed in two of the three. The three workers also went to the hospital the next day and were admitted. All eight workers had elevated mercury in the blood (>5 µg/dL) and/or urine (>25 µg/dL) and were diagnosed with acute mercury poisoning. Initial computed tomography (CT) findings were obtained 36–48 hours after exposure. Early, abnormal CT findings in some patients comprised ground-glass opacification, alveolar consolidation, and ill-defined centrilobular nodules. The latter was the most frequent CT finding (63%). Abnormal findings disappeared after a relatively short time in all patients, and clinically, all patients made a complete recovery without chelation. The authors suggest that most of the interstitial changes following acute mercury vapor exposure are inflammatory edema and are reversible, especially when exposure is relatively mild.

Yoshida et al. (1999) present what they believe is the first report of amalgam allergy associated with aspirin-intolerant asthma. A 36-year-old woman had been diagnosed three years earlier with non-atopic bronchial asthma of unknown etiology. For one month prior to her referral, she experienced nocturnal cough, shortness of breath, and wheezing, which had not responded to treatment. The patient reported having an amalgam filling placed about one month before the asthma exacerbation, and the local gingiva had become swollen the next day. Patch-testing elicited reactions to dental alloys, but not to individual components of the amalgam. The alloys were removed from her mouth. Two days later, despite no change in treatment, her condition improved and stabilized at the level maintained before the filling was placed. The authors state more studies are needed to determine the reason for the reaction (e.g., unknown minor component of amalgam, unknown interaction between components, or differences in allergic reactions between lung and skin).

Summary of Case Studies Related to Effects of Mercury on the Pulmonary System

The results of direct inhalation of high concentrations of mercury vapors ranged from shortness of breath, cough, pharyngitis, and pneumonitis to abnormal CT findings including ground-glass

opacification, alveolar consolidation, and ill-defined centrilobular nodules. The apparent allergy to dental amalgam alloys resulted in cough, shortness of breath, and wheezing.

Case Studies: Effects of Mercury on the Gastrointestinal System (1)

Cummings & Rosenman (2006) present a case study of a 48-year-old male electrician in an electroplating plant who had flare-ups of ulcerative colitis within 24 hours of exposure to mercury vapor during mercury-block maintenance work. The ulcerative colitis would subside in several days, and then return with re-exposure 10 months later. The patient and two of his coworkers were evaluated for mercury exposure. On the day before his maintenance work, the electrician's mercury exposure was measured as 0.11 mg/m^3 as an 8-hour time-weighted average. On the day of maintenance, exposure outside the helmet was 0.41 mg/$m^{3;}$ inside the helmet, 0.10 mg/m^3. Other direct readings indicated high exposures where mercury was stored or dispensed, where respirators were stored, and on the respirators themselves. There was also visible mercury contamination (small droplets of mercury) in the same locations and open containers of mercury in the workplace. Three months after he last performed the maintenance, the electrician had a urinary mercury concentration of 50 µg/L, while his coworkers had normal urinary mercury concentrations. The authors do not know why he had elevated concentrations while the coworkers did not, but they suggest the reason may have related to personal factors such as spending more time in contaminated areas. They also suggest his ulcerative colitis may have been a factor, as could the sulfasalazine treatment he was on for his condition, each possibly causing increased absorption of ingested mercury through his abnormal intestinal mucosa. They note that their report may indicate that mercury vapor exposure is another potential cause of exacerbations of ulcerative colitis.

Case Studies: Effects of Mercury on the Musculoskeletal System (1)

Nadorfy-Lopez et al. (2000) present a case study on the possible effects of chronic mercury exposure on skeletal muscle. Six women aged 36–55 were studied; five were dental technicians and one a dentist. All subjects had been handling mercury for > 16 years, and all presented with some of the clinical symptoms of mercurialism - headache, hair loss, muscular pain, tiredness, dermatitis, nausea, vomiting, mood changes, loss of libido, memory disturbances, and visual alterations. The dental technicians had all retired from work at least for a period of time, and three of them were treated with a chelator. The urinary mercury concentrations of the six women ranged from 13 µg/L to 67 µg/L, and one woman's urinary mercury concentration was 140 µg/L seven years earlier. Needle biopsy was taken from their quadriceps femoris muscles and samples prepared for light microscope histochemistry and for transmission electron microscopy. Selective atrophy of type IIB muscle fibers was found, and in one patient, there was fiber grouping. A mechanism of mercury action is believed to be its high affinity for the sulfhydryl groups of protein. The authors speculate that mercury affects structural protein transport processes and inactivates various enzymes. They conclude that chronic exposure to mercury vapors in dental personnel was associated with muscle damage in the five patients with the highest concentrations of urinary mercury.

Case Studies: Mercury Poisonings (Acrodynia: pain in the extremities) (5)

Five case studies discuss various forms of elemental mercury vapor poisoning and adverse outcomes attributable to high level exposure from various sources.

Abbaslou and Zaman (2006) present a case study of a 10-year-old boy who became ill following 20 days of exposure to elemental mercury, which had been purchased in a traditional store and brought to the home. The boy was attracted to it, and the parents did not know it was toxic and did not report the exposure to doctors when he became ill. The child was referred to the hospital with bloody diarrhea, severe bone pain, paresthesia, papular rash on extremities, generalized itching, excessive perspiration, irritability, palpitations, and insomnia. With only Tylenol prescribed for bone pain, the boy's situation worsened, and he developed back pain and seizures. He was treated for seizures for about 30 days and then developed transient blurred vision, headache, diplopia, and hypertension. A brain MRI demonstrated multiple supratentorial hyperintense lesions. Upon questioning, the mercury issue was raised, and laboratory tests confirmed mercury exposure, with a whole blood mercury concentration of 27.7 µg/L and a 24-hour urinary mercury concentration of 34.4 µg/L. After 9 months of treatment with D-penicillamine, a chelator, the patient's clinical condition and mercury concentrations returned to normal and MRI images improved.

Cherry et al. (2002) present a case study of a 3-year-old girl who developed signs and symptoms of mercury poisoning, which led to an investigation of the six other family members who, although asymptomatic, also had high concentrations of mercury in their urine. The source was determined to be mercury in the carpet, possibly spilled when the previous tenants moved out. The child was referred to hospital admission with progressive weight loss, limping, ataxia, irritability, screaming, regression in speech capability, flu-like symptoms, and a tremor when awake. Her blood mercury concentration was 295 µg/L. [In adults, some neurological functions have been shown to be impacted at urinary mercury concentrations of 25-30 µg/L]. Mean total mercury concentrations in blood in the general population reported in the 1999 ATSDR Toxicological Profile for Mercury were 1-8 µg/L; the arithmetic and geometric mean blood concentrations for dentate women in the U.S. was 2.02 and 1.04 µg/L, respectively (Dye et al., 2005)]. After 24-hour urine collection, the patient had chelation therapy with DMSA, and all family members subsequently had chelation treatments. The patient gradually improved after 4 months, after which all signs and symptoms of toxicity had resolved. Neither the patient nor the household members had neuropsychiatric testing. The authors conclude that the patient suffered for months because of lack of education about mercury toxicity, delayed recognition of mercury poisoning by her physician, and difficulty gaining access to resources. [Note: There are references to a table for results of 24-hour urine collection of all members of the family, but the table does not appear in the article.]

Solis et al. (2000) present the case study of a 45-day-old girl and a 13-month-old boy admitted to hospital with respiratory symptoms and mild hypoxemia. Within 24–36 hours of admission, both children developed signs of respiratory failure and required mechanical ventilation. Investigation revealed the parents were attempting to extract gold ore using liquid mercury six hours before the onset of their children's symptoms. Both parents and the youngest children were in a poorly ventilated kitchen during this process, while the remaining four children were

in rooms adjacent to the kitchen. Urinary mercury concentrations proved mercury exposure in both children, and both received chelation therapy. The infant girl recovered and was discharged on hospital day 25 in excellent condition. After a protracted hospital stay, the 13-month-old boy suffered a cardiopulmonary arrest on the 25th day of hospitalization and died. Forty-eight hours after exposure, the 38-year-old mother presented in hospital with severe respiratory distress. She was intubated and admitted with a diagnosis of pneumonia, and a spot urinary mercury concentration proved to be elevated. She underwent chelation, corticosteroid therapy, and maximal supportive therapy, but died on the tenth day of hospitalization. The 58-year-old father was admitted to a medical center with a sore throat and nonproductive cough 96 hours after the exposure to mercury vapor. Although his urinary mercury concentration was high, he refused chelation therapy and was discharged. He now has periods of confusion, memory loss, insomnia, and persistent cough—signs consistent with mercurialism. The four remaining children (ages 3, 7, 10, and 14) were evaluated and found to have sore throat, nonproductive cough, and headache. Their urinary mercury concentrations were elevated, and all had chelation treatments. One month after discharge, there was no evidence of chronic mercury toxicity. The authors point out the clinical course and outcome of acute mercury vapor poisoning is both varied and unpredictable. While DMSA is not formally approved for mercury poisoning, they find it to be an excellent chelator. Adjunct therapy, such as corticosteroids, requires further testing before they can be recommended.

Torres et al. (2000) observed two children in the same household with symptomatic arterial hypertension simulating pheochromocytoma (tumor of the adrenal). One of the children, a 4-year-old boy, presented in an emergency department with new-onset seizures, anxiety, irritability, tremors, rash, dry lips, excessive sweating, and painful extremities. After elevated concentrations of mercury in urine were identified, an evaluation of the family found similar findings of rash and hypertension in a foster sister. With chelation and treatment for high blood pressure, urinary mercury concentrations decreased, and both children improved. The authors' Medline search for mercury intoxication with hypertension found six reports of patients ranging from 11 months to 17 years. All patients showed symptoms of acrodynia. Three of the children had contact with elemental mercury from a broken thermometer, two had played with metallic mercury, and one had poorly protected occupational exposure. All responded to chelation therapy.

Vardhan and Garg (2005) provide a case study of a 26-year-old dental hygienist with five years of service who was making dental amalgams 3½ years without taking universal precautions. He was hospitalized with a two-day history of irregular, low-grade fever and left-sided pleuritic chest pain. A week after admission, he developed an abscess over the right forearm that required incision and drainage. The wound drained pus mixed with metallic mercury globules (1.5 ml weighing 20 g). This established a diagnosis of chronic elemental mercury poisoning resulting from inhalation of elemental mercury vapors during preparation of amalgams. He received chelation therapy with D-penicillamine, which is known to give variable results, and showed clinical improvement. The author speculates that mercury was disseminated to subcutaneous tissue and the abdomen after being absorbed from the alveoli. The biological plausibility of this mechanism needs to be carefully considered.

Summary of Case Studies Related to Mercury Poisoning (Acrodynia)

Acute mercury inhalation exposure tends to occur in three settings; namely, industrial accidents (61%), novice attempts to extract precious metals from amalgams (24%), and home accidents (15%) (Hsu et al. 1999). The five case studies above discuss various adverse health outcomes resulting from exposure to elemental liquid mercury and inhalation of mercury vapor. The signs and symptoms varied from rash, irritability, and diarrhea to hypertension, seizures, respiratory failure, and death. Two of the individuals in one case study (one child and one adult) eventually died, apparently as a result of a single, intense exposure to mercury vapor. A case in which a dental professional presenting with subcutaneous deposits of liquid mercury after several years of vapor inhalation must be carefully interpreted. The case studies do not address possible long-term effects of low-level exposure to mercury as occurs with dental amalgam.

Case Studies: Effects of Chelation Agents on Removal of Mercury (3)

Chelation intervention was attempted in 3 case studies of elemental mercury exposure – 1 via deliberate intoxication, 1 via accidental intoxication, and 1 related to dental amalgam.

Eyer et al. (2006) report on the quantitative changes of mercury in serum and urine during therapy with chelation agents. Their case involves a 27-year-old man who injected about 1.5 mL of elemental liquid mercury in a cubital vein in a suicide attempt. Upon hospital admission 13 hours later, he complained of chest pain, increased sweating, and tingling in an arm. He had tachycardia, and a CT scan of the thorax and abdomen confirmed deposits of mercury in the capillaries of the lungs, right ventricle, coronary artery, both liver lobes, intestinal wall of the colon, and renal pelvis. Mercury serum concentration on admission was 172 µg/L. Chelation therapy was started 37 hours after the mercury injection using oral DMPS and continued for 5 days. After treatment was stopped for 3 days, therapy proceeded with DMSA for another 5 days, with a total of 3 mg of mercury being excreted. In a follow-up evaluation 66 days after the mercury injection, mercury concentrations in serum and 24-hour urine were 190µg/L and 589 µg/L, respectively; that is, there was no significant change in concentrations in spite of chelation treatment. The authors conclude that although treatment with DMPS or DMSA was associated with marginally increased renal excretion of mercury, clinically relevant elimination did not occur, and evidence of benefit is doubtful.

Forman et al. (2000) present what they describe as the largest published clinical case series describing the use of oral DMSA for treatment of overexposure to metallic mercury in children. In this case, nine children in one family played with mercury from a vial over a period of several days in their apartment. The children, who were asymptomatic, demonstrated pretreatment urinary mercury concentrations ranging from 61 to 1,213 µg/g creatinine, with a geometric mean of 214.3 µg/g creatinine [278 µg/L]. They underwent chelation with DMSA for 5 days, and the geometric mean rose by 268% above baseline to 573.2 µg mercury/g creatinine. The children were discharged and continued to receive DMSA at home for two additional weeks. Six weeks after discharge, all nine children showed reduced urinary mercury concentrations ranging from 71 to 239 µg/g creatinine. An additional two-week course of DMSA followed for

all nine children. Urinary mercury concentrations obtained several months later had dropped to 27.4μg/g creatinine. Two children still had concentrations over 50 μg mercury/g creatinine, and they received a final course of chelation. The authors believe children with urinary mercury concentrations greater than 50 μg/g creatinine should be considered for oral chelation even if they are asymptomatic. No side effects from chelation treatment were observed.

Torres-Alanis et al. (2000) evaluated the effects of intravenous DMPS on urinary excretion of essential trace elements in subjects who received the chelating agent for a mercury challenge test. The subjects were eight women and three men who sought medical attention because of concern with adverse effects attributable to mercury released from dental amalgam fillings. The study sought to identify the potential toxicity and interactions of DMPS on urinary excretion. The study observed excretion of mercury, copper, zinc, selenium, magnesium, manganese, molybdenum, chromium, cobalt, and aluminum. In all the subjects, the therapeutic DMPS dose led to a significant increase in mercury excretion (3- to 107-fold). Urinary excretion of molybdenum, cobalt, and aluminum was too low to permit reliable measurements before or after treatment. Urinary chromium and manganese were unchanged after DMPS. Urinary copper, selenium, zinc, and magnesium increased in most subjects. The authors speculate that DMPS may interact with trace elements, and the importance of this interaction for the potential toxicity of this compound should be studied in more detail.

Summary of Case Studies Related to Effects of Chelation Agents on Removal of Mercury

DMPS and DMSA, given as chelation therapy to an adult male who had intentionally injected mercury intravenously, only marginally increased excretion of mercury and evidence of benefit was considered doubtful. In the case of asymptomatic children accidentally exposed to mercury and treated with oral DMSA, the authors report this chelating agent to be an effective treatment without side effects. The third case study raises questions as to whether DMPS may interact with and alter trace element metabolism, and recommends further study. It appears from this very small sample that, with the possible exception of intravenous injection of elemental mercury, chelation therapy can be effective in mobilizing and excreting mercury.

VI. Data Gaps

1. Very few well-controlled animal studies or human clinical or epidemiological studies exist which evaluate the potential effects of low-level mercury vapor (levels released by dental amalgam for an extended period) exposures on:

    a. Adverse reproductive effects and outcomes and developmental effects in offspring exposed to mercury from maternal amalgam bearers. While there are some studies suggesting that exposure to mercury vapor at the levels associated with dental amalgam does not adversely affect reproductive function, there is a dearth of information concerning the effects of prenatal and/or postnatal exposure from maternal sources of mercury vapor at relevant concentrations. Given the potential of developing organisms to be more sensitive than adults to some chemicals, more research is needed to explore the effects of relevant exposures to mercury vapor on developmental processes.

    b. Allergy or autoimmune diseases. While it seems clear that certain individuals are allergic to mercury in one or more its forms, the percentage of the general population that exhibits such sensitivity was not reported.

    c. Adverse outcomes in children less than 6 years old and pregnant women.

        i. The FDA recommends continued funding by NIH for research on the two prospective clinical trials in children (the New England and the Portugal clinical trials). These studies included children with amalgam and composite restorations placed as early as 6 years of age who were followed with periodic neurologic and renal status assessments on each group through five years (New England) and seven years (Portugal) and information is needed over the longer-term. The two studies reduced some of the uncertainties for outcomes resulting from post-natal exposure to mercury from dental amalgam.

        ii. Additional studies should be undertaken to explore the effects of relevant fetal exposures (gestational exposures from maternal sources) on developmental outcomes in offspring.

2. Given the chronic nature of exposure to mercury vapor via dental amalgam placement, there is uncertainty surrounding the health impact of the very short-term, albeit higher, concentrations of mercury vapor generated during amalgam placement and removal. Studies on the effects of these short-lived elevations in mercury vapor exposure, particularly as they relate to exposures in utero, may provide useful information. However, given what is known from occupational exposures to levels of mercury vapor that are much higher and longer in duration than those likely to be associated with dental amalgam manipulations, concern here is tempered.

3. Well-controlled studies to investigate the effects of co-exposures to mercury vapor via inhalation and dietary methylmercury would provide information to assess whether co-exposure results in neurotoxicity or nephrotoxicity that is additive or synergistic. The effects of co-exposure on developmental neurotoxicity and/or adverse neuropsychological effects should also be evaluated. Recent data suggest that mercury from amalgam fillings contributes little to mercury concentrations in hair, whereas fish consumption does. Mercury from amalgam contributes greatly to urinary mercury concentrations, whereas fish consumption does not. Thus, it appears that hair concentrations of mercury may better reflect exposure to organic forms of mercury and urinary concentrations may be better metrics of inorganic mercury exposure.

VII. References – Master Reference List for Addendum Literature Review

Each citation is assigned a code to identify literature database search origin and, if needed, a rationale for exclusion:

NDB = New databases searched to complement PubMed literature search in 2006 White Paper
CR = Case reports/studies search
CR-Epi = Epidemiology studies identified in case reports/studies search
PC = Publications identified within FDA Public Comments docket
DNR = Did not review – brief rationale

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