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FDA Update/Review of Potential Adverse Health Risks Associated with Exposure to Mercury in Dental Amalgam

National Center for Toxicological Research
U.S. Food and Drug Administration
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Note: This scientific assessment is being released as a draft for the purposes of peer review.

I. Executive Summary

Background

Elemental mercury and inorganic mercury have been demonstrated for decades to be well-known toxicants in both laboratory animal and human epidemiological studies. In studies of workers in various occupations, mercury vapor, depending on the degree of exposure, can cause neurobehavioral changes, cognitive changes and kidney injury. Many of the preclinical and clinical effects associated with neurologic and renal endpoints have been reported at air mercury concentrations ≥ 50-100 ug/m^3 (associated urine mercury concentrations 50-100 ug/g Cr).

Dental amalgam is a restorative material that contains approximately 50% mercury in the elemental form. Mercury vapor is released from amalgam restorations, especially during mastication and brushing. In numerous studies, a positive correlation has been shown between the levels of mercury in blood, urine, and tissues and the number of amalgam restoration surfaces. Exposures to mercury vapor from dental amalgam in the general population not occupationally exposed to mercury are considered to be in the exposure or dose range where associations with adverse human health effects have not been observed. Since the number of individuals with dental amalgam restorations is extremely high (tens of millions annually in the U.S.), a large number of individuals are exposed to this source of mercury.

Charge

In order to address recent concerns related to adverse health effects of dental amalgam, the FDA Associate Commissioner for Science in May 2006 charged the Acting Director of FDA's National Center for Toxicological Research (NCTR) with preparing an assessment of the state of the science regarding the potential health risk of mercury in dental amalgam and to present the assessment to the Medical Devices Advisory Committee and the Peripheral and Central Nervous System Drugs Advisory Committee in September 2006. The purpose of the assessment is to determine whether peer-reviewed literature published since 1997, when the U.S. Public Health Service update report on amalgam was released (USPHS 1997), substantially changes the comprehension of the health risk of mercury in dental amalgam. Using recent reviews conducted by other US government agencies including the Agency for Toxic Substances and Disease Registry (ATSDR - 1999, 2005) and the Environmental Protection Agency (EPA - 2002) and relevant additional peer-reviewed research studies, NCTR scientists were charged with providing an assessment and conclusions regarding significant new information and health risks from mercury in dental amalgam. Specifically, what contributions have peer-reviewed studies published after 1997 made to the understanding of human health risks posed by exposure to mercury in dental amalgam?

Process

The previous reviews of the scientific literature pertaining to health risk from mercury in dental amalgam conducted by U.S. government agencies and international bodies were used as the foundation upon which to build the present literature review. The approach was to build on these previous reviews, rather than duplicate these previous extensive efforts. Consequently, the majority of the present review focused on the in-depth evaluation of 34 peer-reviewed, primary research studies selected for their scientific merit and their potential to provide the most

significant and new information regarding health risks associated with exposure to mercury vapor.

Conclusions

The reviews of the scientific literature on mercury undertaken by ATSDR and EPA are considered highly relevant for assessing the potential risks associated with exposure to dental amalgam mercury. The ASTDR Minimum Risk Levels (MRLs) for chronic elemental and inorganic mercury exposure derived in 1999, and the EPA Reference Concentration (RfC) for mercury vapor and Reference Dose (RfD) for mercuric chloride derived in 1995, have remained unchanged through 2006 and represent chronic and lifetime exposures considered to be highly protective of human health. ATSDR also considers that the MRL for elemental mercury, while derived from exposures in an adult worker cohort, uses a standard uncertainty factor approach to ensure that it is protective for adverse effects in any sensitive subpopulation, such as neurodevelopmental effects in developing embryos/fetuses and children (ATSDR, 1999). The health effects-based exposure reference values derived by ATSDR and EPA in these recent reviews were compared to generally-accepted estimates of exposures to mercury from dental amalgam and resultant urinary mercury concentrations. The exposures to mercury (primarily mercury vapor)in persons with dental amalgam restorations are not expected to exceed these health-based comparison values other than in rare cases with a very high number of amalgam surfaces, and in all cases are well below the mercury exposures observed to have adverse health effects. Thus, mercury exposure from dental amalgam is not believed by USPHS agencies and WHO to represent levels associated with adverse health effects in humans, including sensitive populations.

While accurate reference data for mercury exposures from dental amalgams are not available for the general population (Dye et al., 2005), data from recent studies on mercury exposure and distribution kinetics evaluated for the present review have provided additional information on expected background urinary levels of mercury in persons with and without mercury amalgams. These recent studies with children and adult cohorts support findings of earlier studies demonstrated that urine mercury levels are generally correlated with number of amalgam surfaces and confirm the long-accepted conclusion that dental amalgams release mercury which is absorbed by the body. Five studies evaluated for the present review also confirmed that, in the general population not occupationally exposed to mercury, average urinary Hg values are in the range of $\leq$ 1-3 ug/g Cr (1.3-3.9 ug/L). The American Conference of Governmental Industrial Hygienists (ACGIH, 2001) has set a workplace exposure limit for mercury vapor to which workers may be repeatedly exposed without expectation of adverse effects. This exposure level is intended to minimize preclinical CNS and renal effects and not affect general and reproductive health or normal development of children. Estimates of urinary Hg values that would be observed at this workplace exposure limit designed to protect human health are 29 ug/g Cr.

Past studies have shown that workers exposed to concentrations of mercury vapor that exceed occupational exposure guidelines exhibit adverse effects, with neuropsychological effects being the most sensitive endpoint. In recent studies evaluated for this review, workers chronically exposed to occupational mercury vapor exhibited neurological deficits at the end of exposure (urine mercury values were ~21 ug/g Cr at time of testing) that improved when subjects were

tested five years after exposure had ceased. In workers occupationally exposed to high levels of Hg vapor (mean peak urine mercury levels of > 600ug/L (>460 ug/g Cr) long-lasting effects on peripheral nervous system function were reported, while most measures from an extensive neurobehavioral test battery did not show any residual effects and there were no findings of effects on tests for dementia and other measures of cognitive function.

Recent studies (several from the same laboratory) that focused on amalgam workplace exposure in dental professionals evaluated neurobehavioral outcomes. Many neurobehavioral indices reported to be adversely correlated (regression analyses) with mercury exposure (urine mercury levels were used as the exposure metric) in studies of dentists and dental assistants have not been shown to be similarly affected in other occupationally-exposed groups characterized by much higher urine mercury levels. The lack of a similar correlation of indices of long-term mercury exposures with neurobehavioral outcomes suggests an absence of dose-response and/or only an effect of current mercury exposure status, which, as indicated by urine mercury levels at the time of testing, are much lower than those reported by others that find no effects of mercury on the same measures. These studies also evaluated the effects of genetic polymorphisms which appear to be associated with alterations in important behavioral responses (nervous system functions) in humans. The degree to which these same polymorphisms might or might not affect a given individual's response to mercury remains unknown, largely because of the shortcomings related to control groups and other deficiencies.

Two recent prospective clinical trials conducted with sensitive subpopulations, i.e., children, and other large retrospective studies in adults provide important and relevant observations concerning the possibility that mercury amalgams might adversely affect health. In sum, the studies evaluated do not support the hypothesis that exposure to mercury via dental amalgam restorations causes adverse biological outcomes associated with neuropsychological function, low birth weight, Multiple Sclerosis and Alzheimer's disease.

Several recent animal studies evaluated for this review demonstrated no developmental toxicity associated with mercury vapor exposures *in utero* that do not also cause maternal toxicity. Exposures to relatively high concentrations of mercury vapor during critical periods of gestation did not result in any significant adverse effects on electrophysiological outcomes in rat offspring when tested as adults. While informative, the data from the recent animal studies offered limited insights into the effects of mercury vapor at the levels experienced by persons with amalgams.

Based on a critical analysis of 34 peer-reviewed scientific articles published primarily since 2003, an evaluation of literature reviews conducted by ATSDR (1999, 2005) and EPA (2002), and the health effects-based exposure reference values derived by those agencies, it is concluded that the peer-reviewed scientific information published since 1997 does not substantially change comprehension of the health risk of mercury in dental amalgam compared to previous analyses performed by USPHS. This conclusion is reached in consideration of the information on mercury exposure from amalgams relative to demonstrated adverse health effect exposure levels and to health-based reference values, and in consideration of the potential for health effects in sensitive populations.

II. Introduction

In the United States, people are exposed to mercury from three major sources: fish (methylmercury), vaccines (ethylmercury), and dental amalgams (elemental mercury in the form of mercury vapor). Exposure to elemental mercury vapor in humans can also occur from accidental intoxication, occupational settings, and magico-religious uses. After inhalation, approximately 70-80% of a mercury vapor (Hg^0) dose is absorbed across the alveolar membranes and enters the systemic circulation. Mercury vapor readily diffuses into erythrocytes and is oxidized by the catalase-hydrogen peroxide complex to divalent mercuric ion (Hg^{2+}). Despite this rapid oxidation and intracellular localization, a fraction of the elemental mercury dose crosses the blood-brain barrier. In neuronal cells, mercury vapor is also oxidized to mercuric ions that are unable to diffuse back across the cell membrane. The mercuric ion is believed to be the proximate toxic species responsible for effects of inhaled mercury vapor, in part, due to its high reactivity with sulfhydryl groups on critical macromolecules. While mercury toxicity has been demonstrated in a variety of organ systems in laboratory studies, the central nervous system (CNS) is generally accepted as the most sensitive target organ to elemental mercury vapor. In studies of workers in various occupations, mercury vapor, depending on the degree of exposure, can cause neurological, cognitive, and behavioral changes, including decreased peripheral nerve conduction velocity, tremors, and excitability. Mercury also localizes significantly in the kidney and adverse renal effects can range from reversible proteinuria to irreversible nephrotic syndrome, depending on the degree of exposure to mercury vapor. Many preclinical and clinical effects associated with neurologic and renal endpoints have been reported with occupational exposures to air mercury concentrations $\geq$ 50 -100 ug/m^3(ATSDR, 1999; Roels et al., 1982; Roels et al., 1987). Urine mercury concentrations associated with this level of exposure are approximately 50-100 ug/g Cr.

Dental amalgam is a restorative material that contains approximately 50% mercury in the elemental form. Mercury vapor is released from amalgam restorations, especially during mastication and brushing. A positive correlation has been shown between the levels of mercury in blood, urine, and tissues and the number of amalgam restorations. One study estimated that for every 10 amalgam surfaces placed, urinary mercury concentrations increase by 1 µg per liter (Kingman et al., 1998). Exposures to mercury vapor from dental amalgam in the general population not occupationally exposed to mercury are considered to be in the range where it has not been possible to demonstrate associations with adverse health effects. Since the number of individuals with dental amalgam restorations is extremely high (tens of millions annually in the U.S.), a large number of individuals are exposed to this source of mercury. Thus, the key question is whether the levels of elemental mercury released from dental amalgams are sufficient to cause adverse health effects other than rare cases of allergic reaction.

II.A. Previous Assessments by U.S. Government Agencies

In order to address these concerns, the Department of Health and Human Services (HHS) – U.S. Public Health Service (USPHS) and the Food and Drug Administration (FDA) evaluated the relevant scientific literature regarding the health effects of dental amalgam and published their findings in the 1993 USPHS Report on Dental Amalgam (USPHS, 1993). The evaluation was updated in a report published in 1997 (USPHS, 1997). Both assessments were based on reviews

of toxicological and epidemiological studies of health effects related to exposures to dental amalgams and of exposures to elemental mercury vapor, the predominant form of mercury released from dental amalgams. Scientists and health professionals from U.S. government agencies (CDC, EPA, NIEHS, NIDR, FDA) and academia with diverse science backgrounds and expertise in toxicology, neurotoxicology, immunotoxicology, and epidemiology contributed to the literature review for the 1993 Report. Scientists and health professionals from CDC, NIOSH, NIEHS, and FDA were responsible for reviewing the literature for the updated assessment in the 1997 Update Report.

After a comprehensive review of the literature, the 1993 USPHS Report on Dental Amalgam provided the following conclusion regarding health risks relevant to FDA policies for dental amalgam:

> *…current scientific evidence does not show that exposure to mercury from amalgam restorations poses a serious health risk in humans, except for an exceedingly small number of allergic reactions.*

The 1997 USPHS report provided the following conclusion, updating the 1993 USPHS conclusion:

> *In 1997, with input from a broad cross-section of scientists and dental professionals within USPHS, the FDA completed a review of nearly 60 studies that were published in peer reviewed scientific literature and were cited by citizen groups that petitioned the agency for stringent regulatory actions against dental amalgam. The analysis of the cited studies indicated that the current body of data does not support claims that individuals with dental amalgam restorations will experience adverse effects, including neurologic, renal or developmental effects, except for rare allergic or hypersensitivity reactions.*

Since publication of the 1997 USPHS Update review and evaluation, other U.S. government agencies have independently evaluated the peer reviewed scientific literature regarding the health effects of, and exposures to, inorganic and elemental mercury that are relevant to the comprehension of health risks associated with exposure to mercury in dental amalgam. These reviews, listed below, provide independent evaluations of the literature and present a credible starting point for identifying information developed since the 1993 and 1997 USPHS reports that is relevant to understanding exposures to mercury in dental amalgam and associated potential health risks.

- In 1999 the Agency for Toxic Substance and Disease Registry (ATSDR) evaluated the scientific literature in the Toxicological Profile for Mercury (ATSDR, 1999) and prepared detailed and peer reviewed toxicological evaluations summarized in a Public Health Statement and in Minimal Risk Level (MRL) derivations for inorganic and elemental mercury.
- In 2002 the US Environmental Protection Agency (EPA) conducted an Integrated Risk Information System (IRIS) Screening-Level Literature Review (EPA, 2002b) and identified several significant new studies potentially relevant to the Reference

Concentration (RfC) derivation for inhalation exposure to elemental mercury; however, EPA chose not to initiate a new evaluation of the RfC. A similar review by EPA of the literature up to 2002 pertinent to the cancer assessment for elemental mercury did not identify any critical new studies.

- In 2002 EPA conducted a Screening-Level Literature review pertinent to the oral Reference Dose (RfD) for mercuric chloride (inorganic mercury) and did not identify any critical new studies (EPA, 2002a). A similar review of the literature up to 2002 pertinent to the cancer assessment for inorganic mercury did not identify any critical new studies.
- In July 2005, as part of a statutory requirement for periodic update evaluations of all ATSDR Toxicological Profiles, ATSDR conducted an updated literature search to identify any studies that might affect conclusions regarding risk from exposure to all forms of mercury (ATSDR, 2005). A similar evaluation was performed by ATSDR in each year since the publication of the 1999 Toxicological profile, with new literature search coverage extending back to 1997. On the basis of standardized review criteria used for all ATSDR Toxicological Profiles and evaluation of studies potentially relevant to toxicity and the potential for human exposure, ATSDR concluded that as of July 2005 no studies were identified that would significantly change their toxicological evaluations for metallic or inorganic mercury. Based on that literature review, ATSDR concluded that an update to their 1999 Toxicological Profile was not needed as of July 2005.

II.B. Charge for New Update Review

Consistent with its ongoing commitment to monitor the state of the science regarding the safety of dental amalgam, the FDA Associate Commissioner for Science in May 2006 requested the Acting Director of FDA's National Center for Toxicological Research (NCTR) to prepare an assessment of the state of the science regarding the potential health risk of mercury in dental amalgam, and to present the assessment to the Medical Devices Advisory Committee and the Peripheral and Central Nervous System Drugs Advisory Committee in September 2006. The purpose of the review is to determine whether peer-reviewed scientific information published since 1997 substantially changes comprehension of the health risk of mercury in dental amalgam.

The charge to NCTR seeks to build upon, rather than duplicate, previous reviews of peer-reviewed scientific literature pertaining to health risk from mercury in dental amalgam. Therefore, the NCTR was charged to:

1) Identify, using literature selection criteria (Appendix A), peer-reviewed studies, if any, from the period not covered by the 1999 ATSDR Toxicological Profile, the 2002 EPA literature review, and the 2005 ATSDR literature review that provide new significant information regarding health risk from mercury in dental amalgam. Significant information is defined as information that is likely to change risk estimates by FDA for the use of dental amalgam

2) Identify, using literature selection criteria (Appendix A) any peer-reviewed studies since 1997 contained in the literature reviews provided by ATSDR, EPA, and any governmental public health ministry, department, or agency that are noted by those reviews to be critical or important studies with respect to comprehension of health risk for inorganic or elemental mercury or to mercury in dental amalgam.

3) Provide critical review of each of the identified peer-reviewed studies with regard to quality and relevance to improve understanding of public health significance by evaluating, for example, study methods, study design, statistical power, and relevance to human health. NCTR may use study reviews already prepared and used by EPA or ATSDR in their literature reviews to avoid duplication of effort.
4) Provide an overall assessment and summary conclusions regarding significant new information since 1997 regarding health risk from mercury in dental amalgam. Specifically, what contributions have peer-reviewed studies published after 1997 made to our understanding of mercury-containing dental amalgams and their potential risk to human health?

III. Update Review Strategy and Process

Other government agencies and international organizations have evaluated the peer-reviewed scientific literature regarding human health effects and exposures to mercury that are relevant to assessing the health risks of mercury in dental amalgam. These reviews provide independent evaluations of the literature and a credible starting point for identifying information developed since the 1993 and 1997 USPHS reports. NCTR scientists were charged with conducting a review that builds upon, rather than duplicates, these previous reviews of the scientific literature. The reviews (publication date) are:

ATSDR Toxicological Profile for Mercury (1999)
ATSDR Update - Mercury Chemical Summaries (2005)
EPA Integrated Risk Information System (IRIS) Screening Level Literature Reviews for 1) Mercury, elemental and 2) Mercuric Chloride (2002)
World Health Organization (WHO) Concise International Chemical Assessment Document (CICAD) - Elemental mercury and inorganic mercury compounds: Human health aspects (2003)

In order to capture relevant studies published since the release of these reviews, NCTR scientists identified peer-reviewed articles published from 2003 up to May of 2006 that were judged to potentially provide significant information regarding health risks associated with mercury in dental amalgam. The period of the search was chosen to overlap with recent reviews by ATSDR and coincide with the publication of the 2003 WHO document and 2002 EPA Screening-Review. Articles were identified through a literature search using the National Library of Medicine PubMed database with relevant search terms (Appendix B). Search terms for mercury were limited to those forms of the metal most relevant to the assessment of dental amalgam safety - mercury vapor, elemental mercury, and metallic mercury. Additional terms were included to focus and limit the search to adverse effects and toxicity associated with exposure to mercury vapor or dental amalgam in animal and human studies.

After reviewing the 911 citations and abstracts initially identified by the search, approximately 200 articles considered to be relevant for the present review were requested for preliminary review. Using the criteria established in the charge, 24 articles (Appendix C) were judged to potentially provide the most significant new information with regard to health risks associated

with mercury in dental amalgam, to be of appropriate scientific merit, and to address relevant mercury exposures. Using the same criteria, 10 additional articles were also selected from the ATSDR 2005 update – Mercury Chemical Summaries- Literature Searches, which contains 43 abstracts of key articles used by ATSDR, and from the reference list compiled by EPA for the 2002 IRIS Screening-Level Literature Review, which contains over 2000 citations on elemental mercury from 1998-2002.

Articles with a primary focus on human studies of occupational exposure to mercury vapor, primarily chloralkali workers and dentists, or exposure to dental amalgam were considered to be the most relevant and applicable for the present review. Data obtained from studies of human cohorts occupationally exposed to mercury vapor are relevant and useful for the assessment of potential adverse health effects from low-level exposure to dental amalgam mercury. Animal studies that evaluated adverse responses and/or toxicokinetics of mercury after mercury vapor exposures, including amalgam, were also considered. The ATSDR and EPA reviews also evaluated inorganic ionic mercury studies (i.e., occupational studies and laboratory animal studies of mercuric chloride exposures) which are relevant because it is generally accepted that elemental mercury vapor and ionic mercury share the same proximate toxic species, i.e., the divalent Hg^{2+} cation.

IV. Previous Reports and Literature Reviews

The USPHS, including the FDA, consider the reviews of the scientific literature undertaken by ATSDR and EPA as highly relevant for assessing the potential risks associated with exposure to dental amalgam mercury. The health effects-based exposure reference values (ATSDR MRLs and EPA RfCs and RfDs) for mercury vapor and inorganic mercury derived from these reviews are applicable to making assessments on the safety of dental amalgam. While intended to be used for health assessments from exposure to agents associated with hazardous waste sites, a comparison of these health effects-based reference values to estimated exposures to mercury from dental amalgam and resultant urinary Hg concentrations assisted USPHS and FDA in assessing the potential for human health effects associated with use of mercury amalgam in dental restorations.

IV.A. ATSDR

In 1999, the Agency for Toxic Substances and Disease Registry (ATSDR) conducted a comprehensive review of the scientific literature on all forms of mercury relevant to human exposures and their associated adverse health effects, and published its assessment in the Toxicological Profile for Mercury (ATSDR, 1999). One outcome of this assessment was the establishment of Minimal Risk Levels (MRLs), which are estimates of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are derived for hazardous agents using an approach that involves identifying a no-observed-adverse-effect-level (NOAEL) or lowest-observed-adverse-effect-level (LOAEL) with application of uncertainty factors (UFs). MRLs are generally based on the most sensitive, non-cancer endpoints considered to be relevant to humans and the choice of UFs considers the potential for sensitive human subpopulations, e.g., infants,

elderly, and those with compromised health. MRLs also employ health protective assumptions such as the assumption when using animal data that, in the absence of conclusive evidence to the contrary, humans are more sensitive than animals to a particular hazardous agent. ATSDR relies on evaluations of cancer risk by other organizations, and so MRLs do not include consideration of cancer effects. MRLs are health guidance values and are intended for use by risk assessors as screening tools when determining whether further evaluation of potential human exposure at hazardous waste sites is warranted, but are not intended to define clean-up or action levels. MRLs do not represent thresholds for toxicity and exposure to a level just above the MRL does not necessarily mean that adverse health effects are expected.

The 1999 MRL for chronic inhalation exposure to elemental Hg vapor was established as 0.2 ug/m^3. This MRL was derived, after considering a large body of literature, from a study of 26 workers exposed to low levels of mercury (0.026 mg/m^3) in three industrial settings for an average of 15.3 years (range 1-41 years) (Fawer et al., 1983). Urinary mercury concentrations in this study averaged 11.3 umol/mol creatinine or Cr (approximately 20.1 ug/g Cr; 26.1 ug/L urine). Continuous exposure was taken into account by converting workplace exposures of 8 hr/day-5 days/week into exposures of 24 hr/day-7 days/week. UFs used in deriving the MRL included variability in sensitivity to mercury within the human population (UF = 10) and the use of a lowest-observed-adverse-effect-level (LOAEL) - in this study, increased average velocity of naturally-occurring hand tremors - instead of a NOAEL. In deriving the MRL, the ATSDR applied a less conservative uncertainty factor for the LOAEL (UF = 3 instead of 10), an approach commonly used when the endpoint is determined to be a less serious effect. Application of the exposure conversions and UFs yielded a tolerable Hg vapor intake concentration of 0.2 ug/m^3 for chronic inhalation exposure. At a ventilation rate of 20 m^3/day for an average adult, exposure at the level of the chronic MRL would result in an estimated dose of Hg of 4 ug/day. This value based on the MRL approximates the estimated daily dose of mercury derived from dental amalgam for the general population in the U.S. and Canada, which is <5 ug/day (ATSDR, 1999; WHO, 2003). The derivation of the ATSDR MRL for chronic exposure to mercury vapor also considered supporting evidence from several more recent studies that showed effect levels and adverse outcomes similar to those reported in Fawer et al. (1983), including Ngim et al. (1992) and Piikivi and Tolonen (1989).

ATSDR updates its Toxicological Profiles on an as-needed basis. According to the update review criteria established for all ATSDR profiles, one of the key determinants of a need to update a Toxicological Profile is whether there are new studies that would substantially change the MRLs for the contaminants considered. ATSDR has evaluated the literature for mercury on an annual basis since the publication of the Toxicological Profile for Mercury in 1999 with the last assessment occurring in 2005. These reviews are routinely conducted using comprehensive literature-search criteria, as is done for all substances that are exhaustively evaluated by ATSDR as part of its core statutory mandate to assess and determine both safety and effect levels for contaminants like mercury. The reviews conducted by ATSDR were independent of the reviews conducted by FDA and EPA (see below).

Updated literature searches performed by ATSDR since the 1999 Toxicological Profile through July 2005 identified studies that were retrieved and examined for information that should be considered when assessing the need to update a Toxicological Profile. Based on the most recent

literature assessment, ATSDR has not identified any new information that would warrant an update to their 1999 Toxicological Profile and thus, has determined that there is no need to change the MRL for any form of mercury. ATSDR continues to monitor studies as they become available to guide decision-making as to when an update of the Toxicological Profile and reassessment of the mercury MRLs would be undertaken.

In conclusion, no studies were identified by ATSDR in independent evaluations of the literature as recently as July 2005 that would substantially change the 1999 ATSDR health-based comparison value (the MRL) that was derived primarily using the key study of Fawer et al. (1983). These recent ATSDR assessments considered all endpoints and all forms of mercury and as a matter of standard practice include particular attention to studies that might cause adjustment of the MRL to ensure that it is protective of sensitive subpopulations.

Relevance to FDA Assessment Needs: The literature reviews and evaluations performed by ATSDR in 1999 and in successive years up to 2005 provide additional assurance that FDA has not overlooked peer-reviewed studies relevant to its assessment. Furthermore, ATSDR's decision to not go forward with a reassessment of the MRLs for elemental and inorganic mercury suggest that no studies have been identified that would substantially change the 1999 ATSDR safety assessment and conclusions (in the form of the MRLs). As part of the present review charge, NCTR has conducted in-depth reviews of several studies that were also identified as important in the ATSDR 2005 literature assessment (see below).

IV.B. EPA

The EPA maintains the Integrated Risk Information System (IRIS) that contains summaries of potential adverse health effects that may result from chronic or lifetime exposures to environmental chemicals. IRIS chemical summaries contain qualitative and quantitative health effects information including reference doses (RfDs) for noncancer health effects resulting from oral exposure, reference concentrations (RfCs) for noncancer health effects resulting from inhalation exposure, and cancer weight-of-evidence (WOE) designations. An EPA reference dose (RfD) or reference concentration (RfC) is defined as the daily exposure to a chemical agent that is likely to be without an appreciable risk of deleterious effects during a lifetime. The IRIS RfC for chronic inhalation exposure to Hg vapor is 0.3 ug/m^3 and was derived in 1995 using the same occupational exposure study (Fawer et al., 1983) and supporting studies, including Ngim et al., 1992 and Piikivi and Tolonen, 1989) used by ATSDR (1999) in deriving the MRL for chronic mercury vapor exposure. Exposure to the RfC of 0.3 ug/m^3 would result in a daily mercury dose of approximately 6 µg/day (ventilation rate – 20 m^3/day). The IRIS RfD for chronic oral exposure to mercuric chloride derived in 1995 is 0.3 ug/kg/day.

In 2000, EPA initiated a program of on-going screening-level review of the scientific literature for each of the chemicals in the IRIS database. The purpose of these reviews is to reach a preliminary determination regarding the likelihood that a toxicological reassessment based on an evaluation of the most current health effects literature could potentially result in a significant change to the existing IRIS toxicity reference values or WOE designations. In addition, the results of the screening-level review provide information for the annual IRIS priority-setting process for identifying chemicals for reassessment. The screening-level methodology is

designed to provide a preliminary identification and characterization of new health effects literature and is not intended to provide a comprehensive or critical evaluation of the new literature (EPA, 2004).

In 2002, EPA conducted a screening-level review as part of that agency's re-evaluation of the health effects literature that might influence the RfC for elemental mercury or RfD for mercuric chloride. Over 2000 studies for elemental mercury published from 1998-2002 were screened. The screening level review identified several studies that could potentially produce a change in the elemental mercury RfC (EPA, 2002b). No studies were identified that would produce a change in the cancer weight of evidence (WOE) designation for elemental mercury, i.e., not classifiable as to human carcinogenicity (EPA, 2002b).

Over 400 studies for mercuric chloride published from 1998-2002 were screened. The literature for mercuric chloride, which is relevant to the assessment of amalgam exposures in that the divalent cation is a shared proximate entity for toxic action in non-CNS tissues (divalent cation does not cross blood brain barrier). The screening-review concluded that there appeared to be no critical studies that could potentially produce a change in the RfD or the WOE cancer designation for mercuric chloride (2002a).

In conclusion, while the 2002 EPA Screening-Review assessments identified several studies from 1998-2002 that could potentially produce a change in the inhalation RfC for mercury vapor, EPA has not yet decided to undertake a reassessment of the RfC for elemental mercury (0.3 ug/m^3; EPA, 2002b) or the RfD for mercuric chloride (0.3 ug/kg/day; EPA,2002a). EPA continues to monitor new studies to help determine when a reassessment of the RfCs and RfDs might be needed.

Relevance to FDA Assessment Needs: The literature screening-review assessments performed by EPA in 2002 provide additional assurance that FDA has not overlooked peer-reviewed studies relevant to its assessment of the potential for health effects from dental amalgam exposures. Furthermore, EPA's decisions in the intervening four years to not go forward with a re-assessment of the RfC for elemental mercury or the RfD for mercuric chloride suggest that no studies have been identified that would substantially change the safety assessment and conclusions (in the form of the RfD and RfCs) developed by EPA. As part of the present review charge, NCTR has conducted in-depth reviews of several studies identified as potentially important in the 2002 EPA literature assessment (see below).

IV.C. Reviews by Non-Government Public Health Organizations

American Conference of Governmental Industrial Hygienists (ACGIH)- 2001

Consistent with the ATSDR and EPA use of the LOAEL workplace exposure concentration of 0.026 mg/m^3 from the Fawer et al. (1983) study for the MRL and RfC derivations, the American Conference of Government Industrial Hygienists (ACGIH) recommended a Threshold Limit Value-Time Weighted Average (TLV-TWA) of 0.025 mg/m^3 for occupational exposure to elemental mercury vapor (ACGIH, 2001). TLV-TWA values represent the workplace air concentration to which workers may be repeatedly exposed (8 hr/day, 5 days/week) without the expectation of adverse effects. The limit established for mercury vapor is intended to minimize

the potential for preclinical CNS and renal effects and to provide a degree of assurance that workers will maintain general and reproductive health and that their workplace exposures will not affect the normal development of their children (ACGIH, 2001). Using a generally-accepted air Hg (ug/m^3): urinary Hg (ug/g Cr) concentration ratio of 1:1.22, ACGIH estimated that a worker exposed to the TLV-TWA for mercury vapor would exhibit urinary Hg concentrations of approximately 29 ug/g Cr (ACGIH, 2001). This value compares to urine Hg levels of approximately 0.7 ug/L (0.53 ug/g Cr) (Dye et al., 2005; Kingman et al., 1998) in persons without amalgam placements and is a level that would not be expected to occur even in persons with a very large number of amalgams. For example, mean urinary mercury concentrations were reported to be 0.81 ug/g Cr (1.03 ug/L) in 75% of women in the US who have approximately 12 restored posterior dental surfaces or less (Dye et al., 2005), 3.2 and 1.5 ug/g Cr in children 5 or 7 years after amalgams placed with approximately ~19 amalgam surfaces (DeRouen et al., 2006; Bellinger et al., 2006), and 3.1 ug/L (2.3 ug/g Cr) in men with ~20 amalgam surfaces (Kingman et al., 1998).

World Health Organization (WHO)-2003

In 2000, the ATSDR was asked by WHO to prepare a Concise International Chemical Assessment Document (CICAD) on elemental and inorganic mercury with a focus on human health effects (WHO, 2003). The resulting report was peer-reviewed by an international panel of experts (WHO, 2003). Conclusions within the report are summarized as follows. For most persons in the U.S. and Canada, the estimated exposure to mercury from dental amalgam is <5 ug/day. The CNS is generally considered the most sensitive target organ to long-term exposure to mercury vapor, and subclinical effects have been reported to occur at workplace air concentrations of ≥ 20 ug/m^3. WHO accepted a tolerable intake for elemental mercury vapor of 0.2 ug/m^3 (as derived by ATSDR). Chronic exposure to mercury vapor may also lead to changes in kidney function, but clinically significant renal effects, as compared to CNS effects, occur at somewhat higher exposures that result in urinary Hg concentrations of ≥ 50 ug/g Cr. Exposures at which adverse effects can occur in other organ systems are less well defined, but likely occur at exposure levels higher than those that result in CNS and renal effects (WHO, 2003).

IV.D. Summary of Previous Agency Reports

The ASTDR MRLs for chronic elemental and inorganic mercury exposure derived in 1999, and the EPA RfC for mercury vapor and RfD for mercuric chloride derived in 1995, are health effects-based exposure reference values that have remained unchanged through 2006 and represent chronic and lifetime exposures considered to be highly protective for human health. ATSDR also considers that the MRL for elemental mercury, while derived from exposures in an adult worker cohort, uses a standard uncertainty factor approach to ensure that it is protective for adverse effects in any sensitive subpopulation, such as neurodevelopmental effects in developing embryos/fetuses and children (ATSDR, 1999). The daily exposure to mercury from persons with dental amalgam (primarily elemental mercury vapor) restorations do not generally exceed these reference toxicity values, and thus is not believed by USPHS agencies and WHO to represent levels associated with adverse health effects in humans. It should be noted that both MRLs (ATSDR) and RfCs/RfDs (EPA) are derived by considering only health risks, not benefits and alternatives. Benefits and alternatives are considered important factors in the USPHS's risk management strategy for dental amalgam, but are not addressed here.

MRLs and RfCs/RfDs identify exposure levels at which adverse health effects are not expected but it is generally acknowledged that these values do not identify where health effects are likely to occur. For example, having an exposure at the MRL is expected to be without risk for adverse effects, but it is not clear at what exposure levels health effects would occur that are above the MRL. Because of the general health-protective assumptions used in the derivation of these values, it is expected that health effects in normal individuals would occur at higher levels than the RfC/RfD or MRL. Effects in sensitive individuals would occur at lower doses than those for the general population, but again the health protective assumptions are intended to place the MRL or RfD/RfC values below the effect levels even for sensitive individuals.

It is furthermore important to note that the mercury exposure levels from dental amalgams do not reach the level of mercury exposure that has been shown to have adverse effect in humans in occupational settings. Urinary mercury concentrations in the study used to derive the ATSDR MRL and EPA RfC for elemental mercury vapor (Fawer et al., 1983) averaged 11.1 umol/mol Cr (27 ug/L, 20.6 ug/g Cr). Normal background urinary mercury levels in the general population without amalgams are considered to be approximately 0.7 ug/L, or 0.5 ug/g Cr (Dye et al., 2005) and with amalgams, 3.1 ug/L or 2.4 ug/g Cr (Kingman et al., 1998). Others have reported background levels for urinary mercury in an unexposed population to be 5 ug/g Cr (WHO, 2003) and 0.6 and 1.8 ug/g Cr in children with no amalgams (Bellinger et al. 2006; DeRouen et al., 2006). Urinary mercury levels found in persons with amalgams generally increase by 1.0-1.8 ug/g Cr for every 10 amalgam surfaces placed (Kingman et al., 1998; Dye et al., 2005). Therefore, even for those individuals with a number of amalgam surfaces at the upper end of the range expected in US populations, the highest urinary value expected would be well below the levels observed to have adverse health effect.

The conclusions noted above in the Toxicological Profile for Mercury (ATSDR, 1999) and earlier in the Update on Dental Amalgam (USPHS, 1997) reflected the need for additional epidemiologic research to help decrease the uncertainties in establishing that the use of amalgam for caries restorations is without appreciable risk. In the 1997 Update on Dental Amalgam, the Public Health Service recommended that the National Institutes of Health, through its National Institute of Dental and Craniofacial Research, among others, support highly-focused clinical research to study potential human health effects of dental amalgam. These efforts have resulted in the publication of the first two randomized clinical trials evaluating the effects of dental amalgam on neurologic and renal outcomes in children (Bellinger et al., 2006; DeRouen et al., 2006). Reviews of these two studies as part of the current charge are found elsewhere in this document (section V.A.4.).

V. Review of Additional Scientific Literature

In response to the charge for the current review, 29 human studies and 5 animal studies were reviewed and evaluated.

*Studies obtained from the ATSDR 2005 Update - Mercury Chemical Summaries.
#Studies obtained from the EPA 2002 Update – Screening-Review Literature Review.

[1]Conversion calculations for urinary mercury concentrations.

V.A. Human Studies

V.A.1. Studies on human mercury toxicokinetics and exposure characteristics

Seven articles addressing aspects of Hg exposure and distribution were identified.

Bjornberg et al., Environ. Hlth. Persp. 113:1381-1385, 2005. Transport of methylmercury and inorganic mercury to the fetus and breast-fed infant. This was a study in a relatively small number of subjects (n = 20) looking at number of amalgam surfaces (mean = 5; range 0 – 24) and total Hg versus inorganic Hg blood levels. All inorganic Hg levels reported were low (mean<0.2 ug/L for cord blood; maternal blood; and infant blood). Total Hg exposure was shown to be greater *in utero* than after birth when exposure presumably continued via breast milk; this was true for both methyl-Hg and inorganic Hg. Breast milk levels of inorganic Hg were about 1/3 those of maternal blood. Infant blood levels of Hg decrease after birth even while breast feeding. Strengths: humans; maternal, infant, and cord blood and milk levels. Weakness: small n (20), low exposures (mean number of amalgam surfaces = 5; range = 0-24); no health outcomes.

[*]Dye et al., Occup. Environ. Med. 62: 368-375, 2005. Urinary mercury concentrations associated with dental restorations in adult women aged 16-49 years: United States, 1999-2000. National Health and Nutrition Examination Survey (NHANES) data were used for this study. Amalgam surfaces were the measure of Hg exposure and the n was large (1,626). Background Hg levels in urine (in persons with no amalgams) was 0.69 ug/L or 0.50 ug/g Cr (this is essentially equivalent to the value of 0.70 ug/L reported for mostly men by Kingman et al., 1998). Urine mercury levels were estimated to increase 1.8 ug/g Cr for every 10 dental amalgam surfaces. Reported that 75% of women in the US have approximately 12 restored posterior dental surfaces or less, and mean urine Hg levels in this group were 0.81 ug/g Cr (1.03 ug/L). These data primarily serve as a reference resource for exposure using the association between number of amalgam surfaces and urinary Hg levels. Urine Hg levels (uncorrected for creatinine) correlated significantly with number of amalgam surfaces, but after correction for creatinine, the correlations were even better, and both are much better than blood levels which are usually not significantly correlated with number of amalgam surfaces. Strengths: large n, well-defined population; reference data set. Weaknesses: does not address any health outcomes.

[*#]Jonsson et al., Toxicol. Appl. Pharmacol. 155:161-168, 1999. A compartmental model for the kinetics of mercury vapor in humans. This study was conducted in 9 healthy volunteers exposed to Hg vapor (median ~400 ug/m^3) for 15 min during light exercise. Participants had no Hg amalgam fillings and no known occupational or other recent exposure to Hg. Expired air, urine and plasma Hg levels were measured. Median pre-exposure plasma Hg levels were approximately 1.33 ug/L and the median amount of Hg excreted in urine over 24 hours was

[1] To convert from **nmol Hg/mmol creatinine** to **ug Hg/g creatinine**, multiply by 1.77.
(Based on 200.6 ug Hg/umol Hg and 113 ug creatinine/umol creatinine.)
To convert from **ug Hg/g creatinine** to **ug Hg/L urine**, multiply by 1.3.
(Based on mid-range of normal human urinary creatinine ~1.3 g creatinine/L urine.)

about 2.3 ug. The data showed that ~70% of an inhaled Hg dose was absorbed. The half-life for a respiratory 'depot' of Hg was ~1.8 days and for an excretion depot was ~63 days. Excretion in urine would not be expected to plateau for several months post-exposure for most subjects. Strengths: human subjects; 24hr urine levels; followed for 30 days. Weaknesses: small n; no health outcomes.

***#Kingman et al., J. Dent. Res. 77: 461-471, 1998. Mercury concentrations in urine and whole blood associated with amalgam exposure in a US military population.** This is a study of dental amalgam exposure in an aged population, 40-78 years old (mean = 52.3 years). The Hg exposure metric is the total number of amalgam fillings and number of surfaces with amalgam. The mean number of amalgam surfaces = 19.9 and the mean total and inorganic Hg levels in whole blood = 2.55 ug/L and 0.54 ug/L, respectively; mean urine total and inorganic Hg levels = 3.09 ug/L and 2.88 ug/L, respectively. Total subjects: 1,127; 95% male Caucasian, 5% African American, no females. A significant correlation was found between amalgam exposure and total and inorganic Hg in urine, with or without corrections for urinary creatinine levels; a weak but statistically significant correlation was found between whole blood and total and inorganic Hg. The results also suggest that on average, each ten-surface increase in amalgam exposure is associated with an increase in urine Hg levels of ~1 ug/L. Strengths: human subjects; large n; correlation of amalgam surfaces with blood and urine Hg levels. Weakness: no effect data (see Kingman et al., 2005).

Luglie et al., Arch. Gyn. Obst. 271: 138-142, 2005. Effect of amalgam fillings on the mercury concentration in human amniotic fluid. This study reported on Hg exposure via dental amalgam in pregnant women. The study also monitored fish consumption; smoking; neurological disease history and liver problems. Hg exposure was measured by the number and surface area of fillings; the average number of fillings was 2.26+/-3.19 in the negative group and 5.32 +/- 3.03 in the Hg positive group. Hg levels were measured in the amniotic fluid. Total subjects were 72 pregnant women with 19 considered to be 'negative' - amniotic fluid Hg levels were <0.08 ng/ml; 53 were considered 'positive' - amniotic fluid Hg levels were >0.08 ng/ml (mean of 0.49 ng/ml). It was found that the number and surface areas of dental amalgam fillings influenced the Hg concentrations in amniotic fluid but not significantly. The report mentions that no adverse outcomes were detected throughout the pregnancies or in the newborns, but no outcomes were specified. Mercury in amniotic fluid has not been validated as a biomarker of exposure or effect. Strengths: human subjects; pregnant women; amniotic fluid levels. Weaknesses: difference in amniotic Hg levels between positive and negative groups was minimal.

Tsuji et al., Environ. Hlth. Persp. 111: 623-630, 2003. Evaluation of mercury in urine as an indicator of exposure to low levels of mercury vapor. This study reviews data from ten other studies using different exposure scenarios to see if urinary Hg can be used as a reliable predictor of airborne Hg exposure. Two studies using exposure via dental amalgam were included (Eti et al., 1995; Khordi-Mood et al., 2001). The overall conclusion was that a correlation between air and urinary Hg does exist at airborne Hg levels of 10-50 ug/m^3. However, authors note that this relationship is only reliable at concentrations 10 ug/m^3 or higher. Below 10 ug/m^3, predicted urinary Hg levels are within background ranges. Authors conclude that urinary Hg is therefore not an accurate metric for understanding the exposure of persons to most environmental air

concentrations, which are typically well below 10 ug/m^3. Strengths: summarizes previous work; human data; quantified exposures. Weaknesses: no effects data.

Vamnes et al., Sci. Total Envir. 308: 63-71, 2003. Blood mercury following DMPS administration to subjects with and without dental amalgam. Hg exposure via dental amalgam was reported as amalgam surfaces. Participants consisted of 19 controls who never had amalgams (mean blood Hg levels of ~2.5 ug/L); 21 healthy persons with amalgams (mean of 43 surfaces; mean blood Hg levels of ~5 ug/L); 20 persons with self-reported symptoms from existing amalgams (mean of 37.5 surfaces; mean blood Hg levels of ~5 ug/L); and 20 patients who had amalgams removed (mean of 48 surfaces removed a mean of 31.5 months earlier; mean blood Hg levels of ~4 ug/L). Persons with amalgams removed about 2.5 years earlier had blood Hg levels that were no different from subjects that did not have amalgams removed. This study evaluated the use of chelation with DMPS (2, 3 dimercaptopropane-l-sulfonate) to decrease blood levels of Hg, noting that urinary Hg levels without chelation are not complete measures of the effects of DMPS chelation of Hg. The blood levels of Hg were virtually identical in healthy subjects with amalgam versus subjects attributing symptoms to dental amalgam and in those individuals with amalgams removed. DMPS caused a brief (~30 minute) decrease (24-30%) in blood Hg levels in all groups; levels returned to pre-DMPS levels within 2 hours. The data show that there is no difference in Hg blood levels in subjects with and without self-reported symptoms thought to be caused by amalgams and that chelation by DMPS is short-lived and has minimal impact on blood Hg levels. Strengths: human subjects; blood levels; chelation data. Weaknesses: no outcomes data.

Summary of the studies on human mercury toxicokinetics and exposure characteristics. The data from these studies provide information on background levels of Hg in urine (0.69, 0.7 and 1.33 ug/L) in persons with no Hg amalgams. In addition, there is good evidence that for every 10 Hg amalgam surfaces placed, urine Hg levels increase by 1 to 1.8 ug/L in adult subjects. Upon inhalation of Hg vapor, approximately 70% is absorbed. Airborne levels of <10 ug/m^3 are not accurately reflected in urine Hg levels, whereas higher airborne levels produce urine Hg levels that do correlate with ambient exposures. Chelation of Hg decreases blood and urine levels by up to 30% but for only a short time after which levels rapidly (within 2 hours) return to pre-chelation values. Removal of a substantial number of Hg amalgam restorations does not result in a large decrease in blood Hg levels, even 2-3 years after removal. And lastly, *in utero* (fetal) exposure to Hg-- presumably via exposure to maternal blood via placental transfer--is greater than postnatal exposure with neonatal Hg levels decreasing after birth even with continued exposure via breast milk. In addition, amniotic levels of Hg do not appear to be good biomarkers for the number of maternal amalgams, at least if there are 5 or fewer fillings.

V.A.2. Studies on Human Occupational Exposures to Mercury Vapor and Outcomes

Twelve articles on populations occupationally-exposed to mercury vapor were identified.

Bast-Pettersen et al., Neurotoxicol. 26:427-437, 2005. A neurobehavioral study of chloralkali workers after the cessation of exposure to mercury vapor. This was a clinical study designed to determine whether there were any lingering neurotoxicities from previous exposure to Hg vapor in 49 male chloralkali workers (13.1 mean years of Hg vapor exposure) at

approximately 5 years (mean = 4.8) after the cessation to Hg vapor exposure. Extensive neurobehavioral assessments were carried out and many are the same or very similar to those utilized in the Echeverria et al., 2005 studies. The mean ages of the 49 chloralkali workers and 49 controls were the same at 46.4 yr. Previous testing of 41 of the 49 workers with mean blood Hg levels of 16.5 µg/g Cr at the time of testing (during the period of exposure) had shown that no effects could be found on most of the standard cognitive, sensory and motor function tests. However, the digit-symbol test did show a decreased performance that correlated with urine Hg levels at the time. When the workers were tested 5 years later there were again no deficiencies in any of the standard tests and the digit-symbol performance had improved. These data indicate that, at relatively low occupational exposures (three to ten-fold greater than that expected from exposure to Hg from dental amalgams), minor deficits produced during exposure ameliorated after exposure ended. Strengths: human subjects; relatively low occupational exposures; longitudinal assessments of affected subjects; large number of outcome variables. Weaknesses: relatively small n.

#Bittner et al., Neurotox. Teratol. 20:429-439, 1998. Behavioral effects of low-level exposure to Hg^0 among dental professionals: A cross-study evaluation of psychomotor effects. This report combined data from six studies of dental workers to obtain an n of 230 (80% male) in an effort to explore the sensitivities of 5 psychomotor tasks: Intentional Hand Steadiness Test (IHST); Finger Tapping; the One-hole Test; NES Simple Reaction Time (SRT) and Hand Tremor. Of the psychomotor measures examined, the IHST showed significant negative associations with log-transformed urinary Hg levels. Urine Hg levels ranged from less than 1 to more than 50 µg/L: there was a binomial distribution with about 50% of the subjects having urine levels below 3.0 µg/L and over 25% having levels above 20 µg/L (93%≤ 55 ug/L). Strengths: human subjects, relevant endpoints, urine Hg levels. Weaknesses: no non-dental professional controls.

#Echeverria et al., FASEB J. 12:971-980, 1998. Neurobehavioral effects from exposure to dental amalgam Hg^0: new distinctions between recent exposure and Hg body burden. This was a clinical study of male dentists (n = 34) and female dental assistants (n = 15) who were assessed using a variety of instruments providing measures of symptom self-reports, mood, motor function and general measures of cognitive function. A key feature of this study was the use of the chelating agent DMPS (2, 3-dimercapto-propane-1-sulfonate) to assess Hg body burden. Pre-chelation urine Hg levels of 0.9 +/- 0.5 ug/L increased 10-fold after chelation to 9.1+/- 6.9 µg/L, suggesting that the body burden of Hg in this population of dental professionals is much higher than that indicated by pre-chelation urine Hg levels. Pre-chelation urine levels were suggested to represent metrics of recent exposures whereas post-chelation levels were suggested to represent longer term exposures (body burdens). Subtle but statistically significant associations were demonstrated for recent Hg exposure and measures of mood, motor function and cognition, whereas Hg body burden was associated with symptoms, mood, and motor function. Strengths: human subjects, relevant measures, pre- and post-chelation urine Hg levels. Weaknesses: no non-dental professional controls; no data on other metals whose pre- and/or post-chelation levels might also affect the reported measures.

Echeverria et al., Neurotox. Teratol. 27: 781-796, 2005. Chronic low-level mercury exposure, BDNF polymorphism, and associations with cognitive and motor function. This

was a very comprehensive clinical study in dentists and dental assistants that reported the effects of a polymorphism in brain derived neurotrophic factor (BDNF) or Hg on motor activity and a variety of psychomotor functions (digit span; hand steadiness; finger tapping; visual reproduction; pattern discrimination; digit-symbol; trailmaking; tracking). When present in the homozygous form in humans, the BDNF polymorphism affects a few of the same neurological functions that are affected in Hg intoxication. The study uses most of the same subjects as the Heyer et al., 2004, and Echeverria et al., 2006 studies. There were no 'non-dental worker' controls and dental assistants were from the same practices as the dentists. The Hg levels are slightly higher in this report than those reported by this group elsewhere (Woods et al., 2005) with dentists (n=194) having urine Hg levels of 3.32 ± 4.87 µg/L (a mean of 16 amalgam restorations) and dental assistants (n=233) having urine Hg levels of 1.98 ± 2.29 µg/L (mean =12 amalgam restorations). Work is cited (Aposhian 1998) indicating that dental groups excrete 10-fold more Hg in urine after chelation with DMPS suggesting that the body burden of dental populations is much higher than that of non-dental populations. The authors found no significant effects of Hg or the BDNF allele on verbal intelligence or reaction times. Significant correlations between Hg levels in urine were found for 9 behavioral measures in dentists and 8 measures in assistants (including visual discrimination, hand steadiness, finger tapping and trail making tests). The BDNF polymorphism was correlated with 4 behavioral measures in the dentists and 3 in the dental assistants. Urine Hg levels and the BDNF polymorphism were both correlated with effects on finger tapping in the dentists as well as hand steadiness and trail making B in the dental assistants. The authors report that several of the tests used (e.g., Trail Making, Hand Steadiness), were affected at quite low urine Hg levels when these or similar tests are normally not affected in industrial settings where worker urine levels of Hg are often much higher (Bast-Petterson et al., 2005; Letz et al., 2000). It seems possible that the observed significance could be due to those subjects having the higher urinary Hg levels. Strengths: human subjects, relevant occupational exposures; extensive and relevant measures for several levels of the neuraxis. Weaknesses: lack of non-dental worker controls could maximize population homogeneity and the dental assistants were from the same clinics as dentists; both of these issues make it impossible to rule out workplace characteristics or exposures other than Hg that may have contributed to their findings; lack of association of effects with any index of cumulative or past peak Hg exposures.

Echeverria et al., Neurotox. Teratol. 28: 39-48, 2006. The association between a genetic polymorphism of coproporphyrinogen oxidase, dental mercury exposure and neurobehavioral response in humans. This was a follow-up clinical study in the same subjects (dentists and dental assistants) used in the Echeverria et al. 2005 study where Hg levels and a BDNF polymorphism were reported to affect some of the same measures of neurological function. In the present study the correlation of a CPOX4 polymorphism or urine Hg levels with a host of neurological endpoints was analyzed. Again, the dentists (n=194; 19 years of exposure) had urine Hg levels of 3.32 ± 4.87 µg/L (a mean of 16 amalgam restorations) and the assistants' (n=233; 10 years of exposure) urine Hg levels were 1.98 ± 2.29 µg/L (mean =12 amalgam restorations). The same correlations between urine Hg level and neurobehavioral measures as reported in Echeverria et al., 2005 were reported. As in the Echeverria et al., 2005 study, it is interesting that these authors report significant effects on motor function and steadiness tests that have not been reported in workers exposed to Hg vapor resulting in much higher urine Hg levels (Bast-Petterson et al., 2005; Letz et al., 2000). Significant correlations were found between urine

Hg levels and 9 neurobehavioral measures in dentists (digit span forward and backward; visual reproduction; symbol-digit; finger tapping dominant, non-dominant and alternate; hand steadiness; and tracking) and 8 measures in assistants (digit span forward; digit-symbol; pattern discrimination; trailmaking B; hand steadiness, finger tapping dominant, non-dominant and alternate; and vibration sensitivity). The CPOX4 polymorphism and urine Hg levels correlated with effects on two of the same measures in dentists and 3 in assistants. Strengths: human subjects, relevant exposures; extensive and relevant measures at several levels of the neuraxis. Weaknesses: lack of non-dental worker controls could maximize population homogeneity and the dental assistants were from the same clinics as dentists; both of these issues make it impossible to rule out workplace characteristics or exposures other than Hg that may have contributed to their findings.

***Elghany et al., Occup. Med. 47: 333-336, 1997. Occupational exposure to inorganic mercury vapour and reproductive outcomes.** This is a small retrospective study (medical record review) of occupational exposure (mean of ~3.2 years with a range of 1-13.3 yrs) to inorganic mercury vapor with n = 65. Forty-six women were exposed to inorganic Hg vapor at concentrations estimated to range from 0.025 - 0.60 mg/m^3 (equivalent to 25 - 600 ug/m^3) with the median exposure estimated at 0.09 mg/m^3 (or 90 ug/m^3). Nineteen controls worked in the same factory but were not exposed to Hg vapor. 104 pregnancies occurred from 1948 to 1977 (72 exposed and 32 controls) and represent the data set. As this was a retrospective study, there were no reported/available urinary Hg levels. Findings: possible association between Hg exposure and risk of adverse pregnancy outcome (congenital abnormality) but this observation was not statistically significant. Incidence was 4.2% (3/72 pregnancies) in the exposed group, 0% (0/32 pregnancies) in the controls and 3% (3/104 total pregnancies) overall. [A recent study (Anthony et al., 2002) reports a congenital malformation rate of 2.7% in a population of over 314,000 natural births]. Strengths: humans; relevant endpoints. Weaknesses: retrospective study from medical records; individual exposure data were incomplete; no urine Hg levels available; small n; significant differences in age between comparison groups; lack of dose-response relationship.

[#]Ellingsen et al., Neurotoxicol. 22:249-258, 2001. Neuropsychological effects of low mercury vapor exposure in chloralkali workers. This study examined 47 male chloralkali workers (an average of 42 years old) exposed to Hg vapor for an average of 13.3. years; referents were 47 age matched controls (equated for alcohol consumption but the chloralkali workers smoked more). At the time of testing, mean urine Hg levels in the chloralkali workers were 5.9 nmol/mmol Cr (= 10.6 ug/g Cr) vs. 1.3 nmol/mmol Cr (=2.3 ug/g Cr) in the referents. Small but significant effects of blood levels of inorganic Hg were seen in the WAIS Digit Symbol and the Benton Visual Retention tests but not in the Static Steadiness (Tremor) test. After controlling for differences in intellectual level, there was a weak but significant association between exposure measures and tests of attention, psychomotor and visuomotor speed, and immediate visual memory span. Strengths: human subjects, relevant endpoints, urine and blood Hg levels, exposure histories. Weaknesses: referent group differed significantly on smoking and intellectual capacity.

Heyer et al., Toxicol. Sci. 81: 354-363, 2004. Chronic low-level mercury exposure, BDNF polymorphism and associations with self-reported symptoms and mood. A clinical study

looking at the correlation of urine Hg levels and a polymorphism (V66M) in the brain derived neurotrophic factor (BDNF) allele on self-reported symptoms and mood. When present in the homozygous form, V66M predisposes humans to many of the same neurological deficits seen with Hg intoxication. The authors hypothesized that this polymorphism might interact with Hg to produce exacerbated neurological deficits. This study apparently used the same male dentists (n = 193) and female dental assistants (n = 230) utilized in other studies conducted by this group (Echeverria et al., 2005 and 2006; Woods et al., 2005). The urine Hg levels reported here are slightly higher than those reported in Woods et al., 2005, with the mean for dentists ~3 µg/L (26 years of exposure) and for dental assistants ~2.2 µg/L (15 years of exposure). The authors present their analysis of self-reported data obtained from questionnaires for evaluating a range of recent and chronic symptoms including mood, physical and other mental status. Three measures in dentists (2 in the predicted or worsening direction) and 13 in dental assistants (11 in the predicted direction) were correlated with urine Hg levels only. For dentists, the measures affected in the predicted direction were today's anxiety and headaches and for the dental assistants the 11 affected measures were today's confusion, anxiety, and headache; recent coordination, memory, stomach, skin; and chronic coordination, depression, memory and skin. Implications concerning the BDNF polymorphism are discussed in the section on human polymorphisms (see Section V.A.5. below). Strengths: human subjects; good n; large number of relevant observations; genetic markers. Weaknesses: lack of non-dental worker controls could maximize population homogeneity and the dental assistants were from the same clinics as dentists; both of these issues make it impossible to rule out workplace characteristics or exposures other than Hg that may have contributed to their findings.

***[#]Letz et al., Neurotoxicol. 21: 459-474, 2000. Residual neurologic deficits 30 years after occupational exposure to elemental mercury.** This study reported findings from subjects exposed to very high Hg levels from an industrial setting (dental amalgam exposures are unknown). Participants included 205 former plant workers with 104 exposed to inorganic Hg. The mean peak urine Hg levels was >600 ug/L. An extensive battery of tests which assessed both peripheral and central nervous system function was used to evaluate participants almost 30 years after the documented heavy exposure when the average age was 71 years. The results showed that exposure to high doses of inorganic Hg can have long-lasting adverse effects, primarily on tests of peripheral nerve function. Postural tremor was assessed by physical examination and accelerometry and was weakly associated with past Hg exposure. Even with the aging participants having documented high Hg exposure, there was no correlation between prior Hg exposure and a variety of tests for dementia and declining cognitive functions. Only industrial exposure was considered in this study and Hg levels were much higher than those associated with dental amalgam. Strengths: human subjects; large n; large number of relevant endpoints. Weaknesses: only very high previous exposures to Hg.

Urban et al., Neurotoxicol. 24: 23-33, 2003. EEG photic driving in workers exposed to mercury vapors. This was a clinical study on the effects of previous exposure to Hg vapor in 24 male chloralkali workers (average age 41.7 years) on photic driving (synchronization of the electroencephalogram (EEG) by visual stimuli) compared to 24 male controls (36.0 years of age) matched for alcohol, coffee, tobacco and licit drug use. Exposure durations ranged from 3 to 33 years (mean 15 ±9.7). Groups differed significantly on alcohol intake, and cigarette use (and age at p = 0.069). Urine Hg levels were reported as "total µg/24 hr". It is not clear whether these are

the same workers studied in their companion paper (Urban et. al., 2003) in which urine Hg levels of 20.5±19.3 μg/g Cr were present at the time of testing. A significant effect on photic driving of the EEG was found in both the plant workers and controls but a clear correlation between 24 hr Hg excretion was not found. Exposed workers had significantly increased photic driving responses compared to the control group, but the control group differed with respect to age (they were 6-7 years younger), alcohol and tobacco use (they drank and smoked less). Strengths: human subjects; relevant endpoints. Weaknesses: important differences between the controls and exposed groups; not possible to determine whether Hg exposure accounted for the observed differences.

Urban et al., Neurotoxicol. 24: 711-716, 2003. Color discrimination impairment in workers exposed to mercury vapor. This was a clinical study on the effects of previous exposure to Hg^0 vapor for almost 15 years (14.7 ±9.7) in 24 male chloralkali workers (average age 42 years) on color vision acuity and discrimination compared to 24 male controls (43 years of age). Urine Hg levels of 20.5 ±19.3 μg/g Cr were present at the time of testing. Color vision discrimination was impaired in the chloralkali workers, particularly with respect to the Blue-Yellow confusion axis test. Urine Hg levels and effects did not correlate or demonstrate a dose-response. Since this was a cross-sectional study, it is not known whether the observed effects at the time of testing could be the result of some previous higher exposures. The authors suggest that, based on their findings and others (Cavalleri et al., Toxicol. Lett. 77: 351-356, 1995 showing no effect on color vision at urine Hg levels of 10 ug/g Cr), a threshold of effect on color vision discrimination occurs at urine Hg levels between 10 and 20 ug/g Cr. Strengths: human subjects; relevant endpoints. Weaknesses: small n; no dose-response; weak relationship of exposure and effects.

Ventura et al., Visual Neurosci. 21: 421-429, 2004. Multifocal and full-field electroretinogram changes associated with color-vision loss in mercury vapor exposure. This was a clinical study in Sao Paulo to determine whether there were any lingering neurotoxicities from previous exposure to Hg^0 vapor in 43 (male and female) fluorescent lamp workers (9.8 ± 3.6 yr of Hg^0 exposure) when tested 5.3 ± 3.2 yr after cessation of exposure. The mean age of the 43 chloralkali workers was virtually identical to that of the 21 controls at slightly over 42 years. Color vision electroretinograms and performance of the Cambridge Colour Test were significantly worse in the lamp workers. Strengths: human subjects; relevant endpoints. Weaknesses: no measures of Hg exposure; no mention of amalgams; impossible to make inferences with respect to Hg exposure.

Summary of studies on human occupational exposures to mercury vapor and neurobehavioral outcomes.

Long-lasting effects from occupational exposures at relatively high levels.
In chloralkali workers and age-matched controls, many of the same outcomes used by Echeverria's dental groups were used. Only performance on the digital-symbol test showed significant effects of Hg exposure at the end of chronic exposure (16.5 ug/g Cr at time of initial testing) and performance on this test improved when subjects were tested five years later, after exposure had ceased. Thus, effects were not seen at urine Hg levels higher than those reported by Echeverria and coworkers and the effects waned with time. In workers exposed to very high levels of Hg vapor (mean peak Hg levels of > 600ug/L), very long-lasting effects on peripheral

nervous system function were reported using postural tremor and accelerometry. Most measures from the extensive test battery did not show any residual effects of exposure and there were no findings of effect on tests for dementia and other measures of declining cognitive function. Since Hg exposures were very high, it is difficult to determine how the findings relate to Hg exposure via dental amalgam.

Other occupational studies have implicated prior exposure to Hg vapor as a causative factor in long-lasting adverse effects on color vision function; however, no biological measures of Hg exposure or amalgams were provided. Studies purporting to show increased photic driving responses in persons previously exposed occupationally to Hg vapor were confounded by the fact that the comparison group differed with respect to age and alcohol and tobacco use (controls were younger and drank and smoked less). Thus, the data did not allow a determination as to whether previous Hg exposure accounted for the observed effects. Additionally, studies suggesting impaired color vision in persons previously exposed occupationally to Hg vapor were confounded by the lack of dose-response relationships (urine Hg levels were obtained at the time of testing). In addition, the reported effects of Hg exposure were not strong. Thus, the data did not allow a determination as to whether previous Hg exposure accounted for the observed effects. There was no association between occupational exposure to Hg and congenital malformations.

Effects in dental professionals:
Chelation of Hg in dental professionals suggests that the Hg body burden in this population of workers is much greater than indicated solely by pre-chelation urinary Hg levels. Many of the neurobehavioral measures reported in several studies of dentist/dental assistant populations as being significantly correlated with Hg exposure (urine Hg levels) have not been shown to be similarly affected in other occupationally-exposed groups where urine Hg levels were much higher. These studies did not include a cohort comprised of non-dental controls. This observation, coupled with a lack of association between the neurobehavioral outcomes and indices of long-term Hg exposures suggests that these effects may reflect confounding of Hg exposure with other occupational exposures, something that this type of study design cannot rule out.

V.A.3. Studies on General Mercury Exposure and Cardiovascular Disease

A single article was identified that focused on the issue of cardiovascular health effects and exposure to Hg (with dentists comprising a majority of the cohort studied).

***Yoshizawa et al., N. Engl. J. Med. 347: 1755-1760, 2002. Mercury and the risk of coronary heart disease in man.** This was a nested, case-control clinical study (Health Professionals Follow-up Study) correlating, using the quintile approach, mercury (inorganic plus organic sources, although not specified) levels in toenail clippings with coronary heart disease in male health professionals (470 out of the total 33,737 subjects had coronary heart disease or were heart attack victims during the 5 years of follow-up). A majority of the subjects were dentists and therefore were assumed to have had occupational mercury vapor exposures. Mercury in toenail clippings reflected both occupational exposure of the dentists and dietary fish intake. The five quartiles had the following median levels of Hg (in ug/g toenail): 0.15, 0.28, 0.45, 0.67, and 1.34. There was a significant correlation between toenail Hg levels and fish (i.e.,

methylmercury) intake, and dentists were found to have significantly higher levels of toenail Hg (0.91 compared to 0.45 ug/g for non-dentists). There were no significant differences between the toenail Hg levels in persons that suffered from coronary heart disease and those that did not. The number of amalgams in subjects was not determined. Based on the data from this report, there was no evidence that, at the exposure levels reported, mercury exposure from multiple sources contributed to coronary heart disease. Strengths; humans subjects; relevant endpoints; large n; longitudinal, case-control study. Weaknesses: toenail Hg has not been completely validated as a biomarker of Hg exposure; Hg exposures were from a variety of sources and included organic forms.

Summary of studies on general mercury exposures and cardiovascular disease. This study was identified and reviewed since a majority of the subjects were dentists; thus, it is significant in that it looked at both elemental and methylmercury exposures. No correlation was found between toenail Hg levels and fish (i.e., methylmercury) intake. There was no evidence of a link between Hg exposure (elemental mercury and methylmercury) and coronary heart disease in this study. However, some recent epidemiological studies in men focused on mercury exposure, primarily methylmercury from fish, suggest that methylmercury is associated with a higher risk of acute myocardial infarction, coronary heart disease, and cardiovascular disease in some populations. While important, the weight of evidence for cardiovascular effects is not as strong as it is for childhood neurological effects and the science is still being evaluated. EPA noted in 2005 that these findings to date and the plausible biological mechanisms warrant additional research in this area (EPA, 2005). However, there is insufficient evidence to determine whether exposures to elemental mercury from dental amalgam are associated with cardiovascular disease. Further, cardiovascular disease has not been an endpoint evaluated in studies of elemental mercury exposure in chloralkali workers or and dental professionals.

V.A.4. Human Amalgam Exposures and Outcomes

Seven reports dealing specifically with mercury dental amalgam exposures and outcomes were identified. Two were very recently published epidemiological studies in children. Three considered data from large populations of adults and two focused on targeted populations: persons with Alzheimer's disease and low birth weight babies.

Bates et al., Int. J. Epidem. 33: 894-902, 2004. Health effects of dental amalgam exposure: a retrospective cohort study. This was a retrospective epidemiology study looking at Hg amalgam in a large number (n = 20,000) of members of the New Zealand Defense Force (85% male). Mercury exposures were quantified using amalgam surface years. No actual Hg tissue levels were reported. There was no association of amalgam exposure with Chronic Fatigue Syndrome, an endpoint of special interest in this population. There was a slight increase [Hazard Ratio (HR) = 1.24, 95% confidence interval 0.99, 1.53, p = 0.06] associated with Multiple Sclerosis but the number of cases was small (7 or 0.035% of their population compared with an incidence of 0.14% for US population). There was demonstration of statistically significant protective effects of amalgam: (HR 0.8 to 0.83, p values from 0.02 to 0.07) for several kidney disorders; for inflammatory responses and toxic neuropathy (HR 0.79, p = 0.04); and a protective effect for adjustment reaction (HR 0.9, p = 0.02). The weight of evidence does not suggest that exposure to amalgam causes significant adverse health effects. Strengths: large n; detailed exposure data; large number of health outcomes. Weaknesses: lack important covariates:

smoking, drug and alcohol history; diet, disease, lead exposure, and perhaps, most importantly, urinary Hg levels.

Bellinger et al., JAMA 295:1775-1783, 2006. Neuropsychological and renal effects of dental amalgam in children: a randomized clinical trial. This was a prospective study with a relatively large sample size (n=534) carried out in US children with no restorations prior to entering the study that were given either Hg amalgam (n=267) or dental composite (n=267) restorations. Subjects were followed for 4-5 years after exposure with a mean of 15 surfaces (range 0-55) restored over 5 years. Only total urinary Hg values were reported (0.9 vs. 0.6 ug/g Cr, amalgam vs. composite) and thus reported levels represent Hg exposure from all sources. Hair levels were also reported. Urinary albumin levels were 7.4-7.5 mg/g Cr and indicated no effect on renal glomerular function. Findings: none of the parameters evaluated reached statistical significance for adverse effects of amalgam exposure (IQ, memory, visuomotor function); furthermore, though not significant, the trends appeared to be in the direction of increased IQ (rather than decreased) with increasing amalgam exposure. Hg levels in urine increased a maximum of 1.5 μg/g Cr when an average of almost 19 new amalgam surfaces were placed (0.8 μg/g Cr per 10 surfaces). This is less than the more than 1.0 μg/g Cr per 10 amalgam surfaces previously reported for adults in other studies (Kingman et al., 1998; Dye et al., 2005). Furthermore, peak urinary Hg levels began to decline in the mercury amalgam group by the end of the study and were ~ 0.5 μg/g Cr greater than the composite group. The peak urinary Hg levels observed in the amalgam group were more than 10-fold less than the lowest urine levels reported to be approximate threshold levels (20 μg/g Cr) for effects on vision and motor tremor (Urban et al., Neurotoxicology 24: 711-716, 2003). Hg levels from the composite control group indicate that more than ½ of the Hg present in the urine is from a source other than dental amalgam. Strengths: human subjects, first prospective randomized clinical trial evaluating dental amalgam; large n= 534 children age 6-10 at first exposure; relevant and well standardized endpoints (IQs assessed 3 times; neuropsychological assessments made 4 times during study). Weaknesses: only 5 years of exposure; earliest exposure to amalgam at 6 years of age.

DeRouen et al., JAMA 295:1784-1792, 2006. Neurobehavioral effects of dental amalgam in children: a randomized clinical trial. A prospective study with a relatively large sample size of 507 children living in Lisbon, Portugal, aged 8 to 10 years at the start of the study and who had no prior restorations. Roughly half had Hg amalgam restorations (n=253) and half had resin composite restorations (n=254). The mean number of surfaces restored was 18.7 vs. 21.3 for the amalgam vs. resin groups, respectively. Follow-up lasted for 7 years. Urinary Hg levels at baseline (presumably values were reported as total Hg, but this was not clear) were ~1.8ug/g Cr for both groups and increased to a max of 3.2 ug/g Cr in those with amalgams; levels remained essentially flat in the composite group. Hg levels in the urine were only minimally increased (0.3 μg/g Cr) over composite controls during a 7 year period (0.2 μg/g Cr per 10 amalgam surfaces). This is far less than the more than the 1.0 μg/g Cr per 10 amalgam surfaces previously reported for adults (Kingman et al., 1998). The peak mercury levels reached in the amalgam group were more than 30-fold less than the lowest urine levels that have been reported as threshold for effects on vision and motor tremor, which are some of the neurological functions most sensitive to disruption by Hg (Urban et al., 2003). The data from the composite controls suggest that more than 2/3 of the Hg present in the urine is from a source other than dental amalgam. Functional domains assessed included memory, attention, and visuomotor and nerve

conduction velocities. Assessments were performed approximately on an annual basis. IQ was assessed at the beginning and the end of the study. There were no statistically significant effects on any of the measures examined: those receiving composite were 50% more likely to need additional restorative treatment than the amalgam group. Strengths: large n = 507 children; randomized clinical trial evaluating dental amalgam; relevant measures; repeated assessments; longitudinal; good study design; follow up was high. Weaknesses: earliest age was 8-10 years at start; only 7 years of follow up.

Factor-Litvak et al., Env. Hlth. Persp. 111: 719-723, 2003. Mercury derived from dental amalgams and neuropsychologic function. The effects of Hg amalgam exposure were studied in 550 adults (38% male) at 30-49 years of age. Dose-response data were examined for the number of amalgams vs. urinary (total) Hg levels (ug/g Cr) and the effects of exposure on neuropsychologic function. Exposure level correlations were examined by stratifying groups into 0; 1-5; 6-10; 11-15; and 16-46 total amalgam surfaces. Total urinary Hg means (in ug/g Cr) ranged from ~0.75 to a ~2.9 (total range was 0.09 – 17.9 ug/g Cr) and the overall mean was 1.7 ug/g Cr. The data showed that urinary Hg levels increase with increasing amalgam surfaces (for each 10 surfaces the urine Hg levels went up between 0.7 and 1.0 μg/g Cr) but that there was no statistically significant correlation between urine Hg levels and verbal/nonverbal memory; attention; psychomotor speed; fine motor coordination; motor strength; grooved pegboard; Trails A and B. There was no evidence that dental amalgams produced neurotoxicity. Strengths: humans; long-term exposures; relevant endpoints; good n (550) and power; attempt to correlate exposure level with effect (dose-response: no association). Weaknesses: cross-sectional study; absence of data on when amalgams were actually placed, removed or replaced, but suspect exposures of 10-20 years.

Hujoel et al., Am. J. Epi. 161: 734-740, 2005. Mercury exposure from dental filling placement during pregnancy and low birth weight risk. This was a population-based, case-control study of low birth weight infants (<2500g; n = 1117) vs. normal weight infants (>2500 g; n = 4468). This study reported Hg exposure as number of amalgam fillings (note that this was not number of surfaces). Data were stratified into 0, 1-4 or 5-11 fillings for dose-response analyses concerning low birth weight. There was no significant association with dose of inorganic Hg (number of amalgam fillings) and low birth weight. Strengths: human subjects, large n; case-control study. Weaknesses: no urine Hg levels.

Kingman et al., Neurotoxicol. 26: 241-255, 2005. Amalgam exposure and neurological function. The data reported here derive from the Clinical Air Force Health Study (AFHS; n=1663 and 986 Controls) and 677 Ranch Hand vets (Vietnam veterans exposed to dioxin). Subjects were all males and the total number of amalgam surfaces was stratified 0-7 (n=615); 8-14 (n=466); 15-23 (n=502); 24-61 (n=445). There was no '0' amalgam surfaces group. Urine Hg levels were not given in this study but can be inferred through the earlier Kingman et al., 1998 study, which indicated urine Hg levels of about 1.0 μg/g Cr per 10 amalgam surfaces. No effects/associations with tremor; coordination; station or gait; strength; sensation; muscle stretch reflexes or peripheral neuropathy at any level of amalgam surface stratification. Study population 'represents a relatively high amalgam exposure group …' compared to similar aged US males (NHANES III). Significant but marginal effects were observed on continuous vibrotactile response, but only in select groups (i.e., in combined non-diabetics and non-diabetic

AFHS controls but not in diabetic RH or among combined diabetics). There was no dose-response in the findings. Strengths: humans subjects; amalgam exposures; large n. Weaknesses: lack of continuous variables (i.e., nerve conduction velocity); lack of dose-response; since urinary Hg levels were not reported, interpretation of findings with respect to Hg exposure was not possible; no female subjects; <5% African Americans.

***#Saxe et al., J. Am. Dent. Assoc. 130: 191-199, 1999. Alzheimer's disease, dental amalgam and mercury.** This was a clinical study conducted in adult male and females to determine whether Hg released through dental amalgam might play a role or contribute to the incidence of Alzheimer's Disease (AD). Regional brain levels of Hg were determined at autopsy in 68 subjects with AD and in 33 controls. Regional Hg levels in the brain did not correlate with the number of amalgams and there were no differences between the AD and the control group with respect to number of amalgams. The authors concluded that the Hg levels were not elevated in persons with AD and that the number of amalgams could not be shown likely to affect the incidence of AD. Strengths: humans subjects, large number for a path/tissue level study, relevant measures. Weaknesses: even with relatively high numbers for a tissue analysis study, the number of subjects was low.

Summary of human amalgam exposures and outcomes. Collectively, these studies provide some of the most important and relevant new observations concerning the possibility that mercury amalgam might result in adverse human health effects in persons with amalgam restorations. The two clinical trials in children also provide data for a very important sensitive subpopulation. The large retrospective studies have large sample sizes. Considering all of the studies, the data do not support adverse effects of mercury amalgam in the groups evaluated. In those studies where a significant association was noted (i.e., and increase in hazard ratio for multiple sclerosis, MS), the number of observations that contributed to the findings was very small. For the MS observation, it was noted that the incidence of MS in the study population was well below that of the general population. In addition, there were significant Hg-related decreases in hazard ratios for several outcomes including kidney disorders, inflammatory responses and toxic neuropathy in the same study. An additional cross-sectional study in adults found no correlation between urine Hg levels and a variety of endpoints assessing several levels of the neuraxis. In the study showing significant correlations between number of amalgam surfaces and decreased vibrotactile response, it was noteworthy that the effect was demonstrable only in select groups. In addition, there were no urine Hg data presented in that particular study, making both interpretation and dose-response analysis difficult; e.g., it is difficult to evaluate the effect of outliers on the associations reported without such data (it is likely that in such a large population there would be persons with unusually high Hg levels). The two clinical trials in children found no correlations between amalgam placements and adverse effects even with extensive and repeated assessments of a multitude of neurobehavioral functions. Additionally, the two studies that focused on specific clinical populations - low birth weight infants and persons with Alzheimer's disease - found no evidence that Hg contributed to either condition. Thus, the weight of evidence from these studies that provide the most relevant data clearly do not support the hypothesis that exposure to mercury via dental amalgam restorations causes adverse biological outcomes.

V.A.5. Human Polymorphisms and Interactions with Urine Mercury Levels. Five studies examined the ability of human genetic polymorphisms to alter biological responses to mercury exposure.

Echeverria et al., Neurotox. Teratol. 27: 781-796, 2005. Chronic low-level mercury exposure, BDNF polymorphism, and associations with cognitive and motor function. This was a very comprehensive clinical study (also discussed earlier under occupational exposures) in dentists and dental assistants that reported the effects of a brain derived neurotrophic factor (BDNF) polymorphism (Val66MET) or Hg on motor activity and a variety of psychomotor functions (e.g., digit span; hand steadiness; finger tapping; visual reproduction; pattern discrimination; digit-symbol; trailmaking; tracking). The study uses most of the same subjects as the Heyer et al., 2004 and Echeverria et al., 2006 studies. There were no 'non-dental worker' controls, and dental assistants were from the same practices as the dentists. There were no significant effects of Hg or the BDNF polymorphism on verbal intelligence or reaction time. In this study, as in the previous work from this group, several quantitative measures of neural function were analyzed. The BDNF polymorphism was correlated with effects on 4 measures in the dentists and 3 measures in the assistants. Both the BDNF polymorphism and urine Hg levels correlated with scores on finger tapping in the dentists and hand steadiness and trail making in the dental assistants. The authors suggest the possibility of additive effects between Hg exposure and the BDNF polymorphism for these measures, implying that persons with the BDNF polymorphism may be at greater risk of Hg effects. Strengths: human subjects, relevant exposures; extensive and relevant measures at several levels of the neuraxis. Weaknesses: lack of non-dental worker controls could maximize population homogeneity and the dental assistants were from the same clinics as dentists; both of these issues make it impossible to rule out workplace characteristics or exposures other than Hg that may have contributed to their findings; lack of association of effects with any index of cumulative or past peak Hg exposures.

Echeverria et al., Neurotox. Teratol. 28: 39-48, 2006. The association between a genetic polymorphism of coproporphyrinogen oxidase, dental mercury exposure and neurobehavioral response in humans. This is a follow-up clinical study in the same subjects (dentists and dental assistants) used in the Echeverria et al. 2005 study where Hg levels and a BDNF polymorphism were reported to affect some of the same measures of neurological function. In the present study, correlation of a CPOX4 polymorphism (alteration in exon 4 of the gene encoding the coproporphyrinogen oxidase enzyme of the heme synthetic pathway) or urine Hg levels with a host of neurological endpoints were analyzed. Again, the dentists (n=194; 19 years of exposure) had urine Hg levels of 3.32 ± 4.87 μg/L and the assistant's (n=233; 10 years of exposure) urine Hg levels were 1.98 ± 2.29 μg/L. The same correlations between urine Hg level and neurobehavioral measures as reported in Echeverria et al., 2005 were reported here. As in the Echeverria et al., 2005 study, it is noteworthy that these authors report significant effects on motor function and steadiness tests that have not been reported in workers exposed to Hg vapor resulting in much higher urine Hg levels (e.g., Bast-Peterson et al., 2005; Letz et al., 2000). Significant correlations were found between urine Hg levels and 9 neurobehavioral measures in dentists (digit span forward and backward; visual reproduction; symbol-digit; finger tapping dominant, non-dominant and alternate; hand steadiness; and tracking) and 8 measures in assistants (digit span forward; digit-symbol; pattern discrimination; trailmaking B; hand steadiness; finger tapping dominant, non-dominant and alternate; and vibration sensitivity). In

addition, the CPOX4 polymorphism alone was associated with 4 measures in dentists (spatial span, pattern memory, symbol digit, vigilance) and 5 in dental assistants (digit span, visual reproduction, symbol digit, simple and choice Reaction Times). Both urine Hg levels and the CPOX4 polymorphism affected the digit rate and digit span endpoint in both dentists and assistants and the Beck's depression factor of 'worthlessness' in assistants. The authors suggest the possibility of additive effects between the CPOX4 polymorphism and Hg exposure which suggests that persons with the CPOX4 polymorphism may be at greater risk for Hg effects. Strengths: human subjects, relevant exposures; extensive and relevant measures at several levels of the neuraxis. Weaknesses: lack of non-dental worker controls could maximize population homogeneity and the dental assistants were from the same clinics as dentists; both of these issues make it impossible to rule out workplace characteristics or exposures other than Hg that may have contributed to their findings.

Heyer et al., Toxicol. Sci. 81: 354-363, 2004. Chronic low-level mercury exposure, BDNF polymorphism and associations with self-reported symptoms and mood. A clinical study looking at the correlation of urine Hg levels and a polymorphism (V66M) in the brain derived neurotrophic factor (BDNF) allele on self-reported symptoms and mood. When present in the homozygous form, V66M predisposes humans to many of the same neurological deficits seen with Hg intoxication. The authors hypothesized that this polymorphism might interact with Hg to produce exacerbated neurological deficits. This study apparently used the same male dentists (n = 193) and female dental assistants (n = 230) utilized in other studies conducted by this group (Echeverria et al., 2005 and 2006; Woods et al., 2005). The urine Hg levels reported here are slightly higher than those reported in Woods et al., 2005 with the mean for dentists being approximately 3.0 µg/L (26 years of exposure) and for dental assistants being approximately 2.2 µg/L (15 years of exposure). The authors present their analysis of self-reported data obtained from questionnaires for evaluating a range of recent and chronic symptoms including mood, and physical and other mental status. They observed 3 significant correlations between the BDNF polymorphism alone (a p value of 0.1 was used based on their *a priori* assumption of direction of effects) and effects on self-reported symptoms and mood in dentists and 7 correlations in dental assistants. Of these, one measure in both dentists and dental assistants (today's anxiety) was also correlated with urine Hg levels. Three measures in dentists (2 in the predicted direction) and 13 in dental assistants (11 in the predicted direction) were correlated with urine Hg levels only. Although it was suggested that persons with the BDNF polymorphism may be at greater risk from Hg exposure, there was only one outcome that correlated with both urinary Hg and the BDNF polymorphism in this study. Strengths: human subjects; large n; large number of relevant observations; genetic markers. Weaknesses: lack of non-dental worker controls; dental assistants were from the same clinics as dentists.

Heyer et al., Toxicol. Lett. 161: 159-166, 2006. A cascade analysis of the interaction of mercury and coproporphyrinogen oxidase (CPOX) polymorphism on the heme biosynthetic pathway and porphyrin production. Participants in this study were dentists (n=80) with mean urine Hg levels of 1.9 +/- 1.8 ug/L and dental assistants (n=98) with mean urine Hg levels of 1.4 +/- 1.6 mg/L. There were no non-dental worker controls and the number of years of exposure to amalgam were not reported here. The subjects are very likely a subset of those in other studies (Echeverria et al., 2005 and 2006; Heyer et al., 2004; Woods et al., 2005).. This work basically revisits earlier work (Woods et al., 2005) but provides a better explanation

of how Hg interacts with CPOX4 to alter heme metabolism. However, there is no explanation of why this would be relevant to any blood disorders or other adverse effects. This manuscript is clinically oriented but is more of a review article about remodeling and refining the ways in which Hg can interact with humans having the CPOX4 allele to affect products and intermediates in the heme biosynthetic pathway. Strengths: human subjects, relevant endpoints; genetic markers. Weaknesses: lack of non-dental worker controls could maximize population homogeneity; dental assistants were from the same clinics as dentists; both of these issues make it impossible to rule out workplace characteristics or exposures other than Hg that may have contributed to their findings; there is no discussion of an association of altered heme synthetic pathways and adverse biological effects.

Woods et al., Toxicol. Appl. Pharmacol. 206: 113-120, 2005. The association between genetic polymorphisms of coproporphyrinogen oxidase and an atypical porphyrinogenic response to mercury exposure in humans. A clinical study in male dentists (n = 252) and female dental assistants (n = 230) to assess the correlation between urine Hg levels and CPOX polymorphisms on an atypical porphyrinogenic response (excess excretion of 4- and 5-carboxyl porphyrins and the atypical ketoisocoproporphyrine (KICP). This study looked at the CPOX4 allele, an isoform present in 15% of all people (but only homozygous in 2%), and how it interacts with Hg to alter heme pathway intermediates/products and potentially dispose people with the CPOX4 polymorphism to reduced heme synthesis capacity and associated build-up of the aberrant CPOX4 metabolite KICP. Data are presented indicating that urine Hg levels and the presence of the CPOX4 polymorphism interact to effect an increase in dehydro-isocoporphyrin and KICP. Urine Hg levels for the dentists (mean = 2.32 μg/g Cr) were quite low; none were reported for the dental assistants. The number of amalgams is not reported in this study. There appears to be a subpopulation of participants with high mercury levels (>20 ug/g Cr). Since there are no non-dental controls there could be another factor(s) that the dentists and dental assistants have in common other than Hg exposures to influence the findings. Strengths: human subjects, relevant endpoints; genetic markers. Weaknesses: lack of non-dental worker controls; dental assistants were from the same clinics as dentists; no discussion of how altered heme synthetic pathways as reported here might lead to potential adverse effects.

Summaries of studies that examined the relationship between human genetic polymorphisms and urine Hg levels to alter biological responses. All of the studies in this section were carried out in the same human subjects or subsets of the same populations. Thus, to varying degrees, they all share different strengths but the same weaknesses. These studies lacked the use of non-dental worker controls, thus the issue of selection bias arises. In addition, the dental assistants chosen as participants were from the same clinics as the participating dentists. There were often no associations between the outcomes of interest and any index of cumulative or past peak Hg exposures. These issues make it impossible to rule out workplace characteristics or exposures other than Hg that may have contributed to the findings from all of these papers. Thus, interpretation of the data for those with dental amalgam restorations is more difficult. Given these deficiencies, it does appear that BDNF and CPOX polymorphisms are associated with alterations in important behavioral responses (nervous system functions). The degree to which these same polymorphisms might or might not affect a given individual's response to Hg remains unknown, largely because of the shortcomings of the available data.

V.B. Animal Studies

V.B.1. Mercury Vapor and Maternal/Reproductive Toxicities

Two animal studies were identified that looked at issues of maternal and reproductive toxicity.

*#**Davis et al., Toxicol. Sci. 59 : 291-296, 2001. Mercury vapor and female reproductive toxicity**. Adult female rats were exposed (nose only) to Hg vapor over postnatal days (PNDs) 80-90. Dose-response (0, 1, 2 or 4 mg/m^3) and time course (2 hr/day for 11 days) data were obtained. Total urinary Hg levels were reported (ng/g) of urine after 11 days of exposure and were dose-related: control values were 0.44 ng/g; at 1mg/m^3, 9.1 ng/g; at 2 mg/m^3, 52.7 ng/g; and at 4 mg/m^3 , 841.6 ng/g. There were no significant effects of Hg vapor exposure on pregnancy rate or number of implantation sites. Estrous cycles were slightly prolonged in the 2 higher dose groups, and progesterone and estradiol levels were significantly different in the high dose group. Kidney Hg levels (0.066, 32, 96 and 142 ug/g for controls, 1, 2 and 4 mg/m^3 dose groups, respectively) were 20-60 times those of brain levels and even at these levels there was no histological evidence of toxicity seen in the kidney. Strengths: some dose-response information; inhalation of elemental mercury which is relevant to amalgam; nose-only exposures eliminates deposition on fur and subsequent ingestion; relevant endpoints. Weaknesses: rodent model; short-term exposures, urine samples were collected immediately after exposures so 24-hr levels are not known; high doses (maternal toxicity occurred at high doses).

Morgan et al., Toxicol. Sci., 66: 261-273, 2002. Deposition of inhaled mercury vapor in pregnant rats: maternal toxicity and effects on developmental outcome. This study employed nose-only exposure of pregnant rats to elemental Hg vapor at 0, 1, 2, 4 or 8 mg/m^3 for 2 hr/day from gestation days 6-15. Hg levels were measured in brain, liver and kidney in both exposed maternal animals and offspring and several other maternal tissues. Hg levels increased in a dose-dependent manner in all tissues. The highest maternal levels were found in kidney (180 ug/g in the highest dose group; control values were 0.023 ug/g). Levels in kidney > lung> brain> liver> uterus> adipose> RBCs> plasma. Exposure decreased maternal body weight, whereas maternal kidney weight increased in the 4 and 8 mg/m^3 dose groups and protein and alkaline phosphatase activity increased in maternal urine. No exposure-related histopathology was seen in lung, kidney or livers of pregnant animals when examined at several time points: gestational days 6 or 15 or postnatal day 1. While Hg levels were demonstrable in fetal tissue, they were much less than maternal levels, suggesting minimal passage across the placenta: maximum fetal levels occurred in the liver and were ~130 ng/g; fetal kidney and brain levels were 65 ng/g and 30 ng/g, respectively. Adverse effects on developmental outcome (increased resorptions; decreased litter size and pup body weights) occurred only at exposure levels that also caused maternal toxicity, i.e., 8 mg/m^3. Strengths: some dose-response information; inhalation of elemental mercury which is relevant to amalgam; nose-only exposures eliminates deposition on fur and subsequent ingestion; relevant endpoints. Weaknesses: rodent model; short-term exposures, urine samples collected immediately after exposures so 24-hr levels are not known; high doses (maternal toxicity occurred at high doses).

Summary of animal studies that looked at issues of maternal and reproductive toxicity. Both studies indicate that there is no development toxicity associated with mercury vapor exposures

that do not also cause maternal toxicity. In addition, maternal toxicities were only noted at very high levels of exposure to mercury vapor ($\geq$ 2 mg/m^3).

V.B.2. Mercury Vapor and Neurobehavioral Outcomes

Three studies were identified that examined the relationship between exposure to mercury vapor and behavioral outcomes.

***Herr et al., Toxicol. Sci. 82: 193-206, 2004. Evaluation of sensory evoked potentials in Long Evans rats gestationally exposed to mercury (Hg^0) vapor.** A rat study providing indirect (transplacental) prenatal exposure to male and female rats by exposing the mothers to 4 mg/m^3 Hg vapor for 2 hr/day over gestation days 6-15, a large part of the gestational period. Offspring (one male and female per litter) were evaluated as adults between at postnatal days 140 and168. Brain Hg levels were not reported for the animals in this study but these animals were given an exposure identical (same lab) to that reported to produce Hg levels of 0.02 ug/g in the brains of offspring at birth (see Morgan et al., 2002, above). Those data showed that very little Hg crosses the placenta into the pups after maternal exposures. In this study here, maternal weight decreased 7% during exposure but offspring weight was not affected out to at least 6 months of age. The neurological evaluations (flash evoked potentials; pattern evoked potentials; compound nerve action potentials; cortical somatosensory evoked potentials; brainstem auditory evoked response; cerebellar somatosensory evoked potentials; nerve conduction velocity) showed no conclusive effects on any measure tested; compound nerve potentials suggested a slight, but not significant, trend toward impairment. The study concluded that there were no effects of prenatal Hg exposure on responses evoked from peripheral nerves or the somatosensory, auditory or visual modalities**.** Strengths: sampled a variety of levels of the neuraxis; mercury vapor was used; gestational exposure; assessed long-term (residual) effects in adulthood (PND 140-168). Weaknesses: rats; high dose exposure.

Yoshida et al., Toxicol. Sci. 80: 69-73, 2004. Susceptibility of metallothionein-null mice to the behavioral alterations caused by exposure to mercury vapor at human-relevant concentration. This study utilized adult female mice with mutant metallothionein genes that are nonfunctional (knocked out - KO) versus animals with wild type metallothionein genes to look at how the metallothionein function affects the neurotoxicity produced by exposure to Hg vapor (whole body immersion) at 0.06 mg/m^3, 8 hr/day for either 12 or 23 weeks. At necropsy, the brain Hg levels in the metallothionein KO mice were 0.66 ± 0.08 μg/g, a level less than that found in the wild type (0.97 ± 0.07 μg/g). KO mice had a higher open field activity and poorer performance in passive avoidance test than the wild type mice. The statistical analysis was inappropriate (used a T-test and not an ANOVA). Hg toxicity and lower brain Hg levels were observed in KO mice compared to wild type mice. Strengths: mercury vapor at relatively low concentrations (60 ug/m^3), chronic exposures; exploration of knock-out effects; functional assessments. Weaknesses: since exposures were whole-body, exposure to Hg could be from mixed routes due to fur contamination and oral exposures (ingestion); no sham/concurrent controls.

Yoshida et al., Toxicol. Lett. 161: 210-218, 2006. Behavioral changes in metallothionein-null mice after the cessation of long-term, low-level exposure to mercury vapor. This study was an adult mouse study very similar to Yoshida et al. 2004 except that Hg vapor exposures (whole

body) occurred 24 h/day for 29 weeks at 0.055 mg/m^3. Evaluations for neurotoxicity occurred at the end of exposure and 12 weeks later and included locomotor activity (open field behavior), learning ability (passive avoidance), and spatial learning ability (Morris water maze). After 29 weeks of exposure, metallothionein knock-out (KO) mice had brain Hg levels of 0.84 +/- 0.04 µg/g while the wild type mice had levels of 1.75 +/- 0.34 µg/g ; 12 weeks later, brain levels were 0.04 +/- 0.01 and 0.10 +/- 0.01 µg/g, respectively. At the end of exposure, locomotor activity was marginally depressed in both strains, while 12 weeks later it was marginally increased in both strains. At the end of exposure, passive avoidance 'retention' behavior was disrupted in both strains and 12 weeks later this effect disappeared but was replaced with a decrease in training latency. Performance of the Morris water maze was not affected at any time point. The authors note their findings were the first to indicate that long-term, low-level Hg vapor can lead to persistent neurobehavioral effects. The effects reported did not follow the prediction that higher brain Hg levels are associated with greater neurological impairments. Strengths: mercury vapor at relatively low concentrations (55 ug/m^3**)**, chronic exposures at 24 hr/day; exploration of knock-out effects; functional assessments. Weaknesses: since exposures were whole-body, exposure to Hg could be from mixed routes due to fur contamination and oral exposures (ingestion); no sham/concurrent controls.

Summaries of studies that examined the relationship between exposure to mercury vapor and behavioral outcomes. Gestational exposures to relatively high concentrations of Hg vapor (4 mg/m^3, enough to cause weight loss in the dams) did not result in any significant adverse effects on a variety of sophisticated electrophysiological outcomes in rat offspring when tested as adults. Studies in metallothionein knock-out (KO) mice exposed chronically to whole body mercury vapor (55 to 60 ug/m^3) indicated differences in sensitivity to Hg vapor compared to wild-type mice; however, the increased neurological deficits observed in KO mice occurred at lower brain Hg levels compared to those observed in the wild type mice. The findings that lower brain Hg levels were associated with a greater degree of neurological deficit and the lack of concurrent controls in this study make the data difficult to interpret. The data from these studies do not provide information useful for addressing issues related to the effects of Hg vapor at the levels experienced by persons with amalgam restorations.

V.C. Summary of the Review of 34 Studies

Consistent with previous reviews (USPHS, 1993; 1997; ATSDR, 1999) of the literature, a positive association was observed between urinary mercury values and the number of amalgam fillings or surfaces placed (Kingman et al, 1998; Factor-Litvak et al., 2003; Dye et al., 2005). Five studies in the present review also confirmed that, in the general population that is not occupationally exposed to mercury, average urinary Hg values are in the range of less than 1-3 ug/g Cr (1.3-3.9 ug/L) (Factor-Litvak et al., 2003; Bellinger et al., 2006; DeRouen et al., 2006; Kingman et al., 1998; Dye et al., 2005). In two studies of dental professionals who placed amalgam restorations, average urinary Hg concentrations were also approximately 2-3 ug/g Cr (Woods et al., 2005; Echeverria et al., 2005).

It is clear that persons chronically exposed to mercury vapor in the workplace can suffer adverse health effects that often manifest as decrements in nervous system function. In some cases, recovery of function occurs after exposure has ended even though the process may take several

years. In cases of very high exposures to mercury vapor, adverse effects may be very long-lived and/or permanent, particularly in the peripheral nervous system. General cognitive function and intellectual capacity appears to be relatively unaffected in such cases. Occupational exposure of dentists and dental assistants to mercury vapor appears to increase Hg body burden that is not reflected in urine mercury levels. The data are not sufficient at present to conclude whether this increase in mercury body burden results in adverse neurobehavioral outcomes. While it does appear that certain polymorphisms are associated with alterations in important nervous system functions in humans, the degree to which these polymorphisms might or might not affect a given individual's response to mercury remains unknown at present.

Clinical trials in children have provided critical observations concerning the effects of exposure to mercury from dental amalgam. Extensive, repeated assessments of a multitude of neurobehavioral functions demonstrated that there were no correlations between amalgam placements and adverse effects. Data from retrospective studies in large populations of adults do not support the finding of adverse effects of mercury amalgam and in a cross-sectional study there was no correlation between urine mercury levels and a variety of endpoints assessing several levels of the neuraxis. In studies of clinical populations, there was no evidence that mercury from amalgams contributed to low birth weight in infants or to Alzheimer's disease in adults. Fetal levels of mercury are generally much less than maternal levels and decrease after birth even when exposure via breast milk continues. The weight of evidence from human clinical and epidemiological studies of mercury amalgam does not support the hypothesis that exposure to mercury via dental amalgam restorations causes adverse biological outcomes.

Data from animal studies indicate that there is no developmental toxicity associated with mercury vapor exposures that do not also cause maternal toxicity. Gestational exposures to relatively high concentrations of mercury vapor did not result in any significant adverse effects on a variety of sophisticated electrophysiological outcomes in rat offspring when tested as adults.

VI. Update/Review Conclusion

Based on an evaluation of the extensive literature reviews conducted by ATSDR (1999, 2005) and EPA (2002), and an assessment of the health effects-based exposure reference values for elemental mercury derived by those agencies and WHO and ACGIH, no information was found that would change the comprehension of health risks for inorganic or elemental mercury and mercury in dental amalgam. In an effort to obtain new information that might improve understanding or change risk estimates for the use of dental amalgam, twenty-four peer-reviewed scientific articles--published primarily since the reviews conducted by ATSDR and EPA--and ten peer-reviewed articles from the ATSDR and/or EPA reviews deemed to contain important and relevant information were critically reviewed. Compared to previous analyses performed by USPHS, no significant new information was discovered from the review of these 34 articles that would change the risk estimates by FDA for the use of dental amalgam.