

Joint Meeting of the Dental Products Panel of the Medical Devices Advisory Committee of the Center for Devices and Radiological Health and the Peripheral and Central Nervous System Drugs Advisory Committee of the Center for Drug Evaluation and Research

September 6, & 7, 2006
Holiday Inn
Gaithersburg, MD



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

Outline

- Introduction and charge for the current review
- Other U.S. government agency evaluations of mercury
- FDA update/review strategy and process
- FDA update/review
 - Assessments of previous government agency literature reviews (ATSDR, EPA)
 - Reviews by non-government public health organizations (WHO)
 - Review of additional scientific literature: Summaries of 34 studies
 - Overall review conclusions

Introduction

- To address recent concerns expressed by some members of the public related to adverse health effects of dental amalgam
- And consistent with FDA's ongoing commitment to monitor the state of the science regarding the safety of dental amalgam
- FDA's National Center for Toxicological Research (NCTR) was charged to prepare a review of the state of the science regarding the potential health risk of mercury in dental amalgam



Introduction (cont.)

- US Public Health Service last reviewed mercury amalgam in 1997
- The purpose of the 2006 review is to determine whether peer-reviewed scientific information published since 1997 substantially changes comprehension of the health risk of mercury in dental amalgam

Specifics of the charge for the review

- Build upon previous reviews by public health agencies
 - no need to duplicate effort
- Identify peer-reviewed studies important to comprehension of health risk for inorganic or elemental mercury or to mercury in dental amalgam since 1997

Specifics of the charge (cont.)

- Provide critical review of each of the identified studies or refer to other public health agency reviews as appropriate
- Provide an overall assessment and summary conclusions
- Specifically, what contributions have peer-reviewed studies published after 1997 made to our understanding of mercury-containing dental amalgam and its potential risk to human health?

Other U.S. Public Health Agency Evaluations of Mercury

- Agency for Toxic Substances and Disease Registry (ATSDR)
 - 1999 Toxicology Profile for Mercury
 - Detailed, peer-reviewed evaluations
 - Minimal Risk Level (MRL) derivations
 - 2000-2005 yearly update evaluations
 - Literature searches to identify studies that might affect conclusions regarding risk and require a Profile update

Other U.S. Public Health Agency Evaluations of Mercury (cont.)

- Environmental Protection Agency (EPA)
 - 2002 Integrated Risk Information System (IRIS) literature reviews for both mercury vapor and inorganic mercury
 - Used to decide whether to update their health-based reference values used in environmental regulatory programs for mercury

FDA Review Strategy and Process

- Identify relevant peer-reviewed articles published from 2003 to May 2006
 - Period overlaps recent reviews by ATSDR and coincides with the publication of a 2003 WHO document and 2002 EPA Literature Review
 - Search terms for dental amalgam, mercury vapor, elemental mercury, and metallic mercury with a focus on adverse effects and toxicity in animal and human studies

FDA Review Strategy and Process (cont.)

- 911 citations identified
- ~200 requested for preliminary review
- 24 judged to provide the most significant new information
 - Acceptance criteria – Appendix A
- No study excluded based on its conclusions
- 10 more selected from 2005 ATSDR update and 2002 EPA IRIS Literature Reviews

Assessments of Previous Government Reports and Literature Reviews

- Provide health effects-based exposure reference values for mercury vapor and inorganic mercury
- Compare reference exposure values and urinary mercury concentrations
- Applicable to making safety assessments for dental amalgam

Notes on Health Based Comparison Values

- Health based comparison values help regulatory and public health agencies make decisions
- EPA and ATSDR values have been derived that are useful for our review
- EPA:
 - Reference Concentration or RfC
 - Reference Dose or RfD
- ATSDR
 - Minimal Risk Level or MRL

EPA RfC and RfD

“In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.”

“In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.”

(source - <http://www.epa.gov/iris/>)

Minimal Risk Levels (MRLs)

“An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure.”

“Although the term, MRL, may seem to imply a slight level of risk, MRLs are, in fact, considered to represent safe levels of exposure for all populations, including sensitive subgroups.”

“MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure.”

(source – 1999 ATSDR Toxicological Profile for Mercury)

MRLs, RfCs, and RfDs:

- Do not represent thresholds for toxicity
- Exposure to a level just above the MRL, RfC, or RfD does not mean that adverse health effects are expected
- Derived by identifying a no-observed-adverse-effect-level (NOAEL) or lowest-observed-adverse-effect-level (LOAEL) and dividing by uncertainty factors (UFs) to protectively account for what is not known

The 1999 ATSDR MRL

- The MRL for chronic inhalation exposure to elemental Hg vapor is 0.2 micrograms per cubic meter ($\mu\text{g}/\text{m}^3$), 24/7
- Exposure at this MRL would result in a dose of about 4 micrograms per day ($\mu\text{g}/\text{day}$)
- This approximates the general population exposure to mercury (inhaled or swallowed) from dental amalgam, which is estimated to range from 1-5 $\mu\text{g}/\text{day}$ (source - 1993 USPHS report)

ATSDR 2005 Update

- Evaluated the Hg literature annually since 1999 with the last assessment occurring in 2005. These reviews are independent of the reviews conducted by both FDA and EPA
- Did not identify any new studies that would warrant an update of its 1999 Toxicological Profile; thus, no need at this time to change the MRL for chronic exposure to Hg vapor

EPA 2002 IRIS Screening-Level Literature Reviews

- “The literature published since the inhalation RfC for elemental mercury was derived (1990) contains study data that could potentially produce a change in the RfC.”
- However, EPA chose not to initiate a new evaluation of the RfC (0.3 ug/m³, 24/7)
- “The literature published since the oral RfD for mercuric chloride was derived (1988) does not appear to contain study data that could potentially produce a change in the RfD.”

Relevance of ATSDR and EPA Reviews to FDA Assessment Needs

- ATSDR MRL and EPA RfC for Hg vapor have remained unchanged through 2006
- Derived to be protective of human health, including sensitive subpopulations
- 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



Reviews by Non-Government Public Health Organizations



World Health Organization (WHO) 2003

- WHO Concise International Chemical Assessment Document (CICAD): human health effects of elemental and inorganic mercury
- ATSDR expert was the lead author
- Peer-reviewed by an international panel of experts

WHO CICAD Conclusions

- Estimated exposure to mercury from dental amalgam is <5 ug/day for most persons in the US and Canada
- Central Nervous System (CNS) considered the most sensitive target for long-term exposure to mercury vapor
- Subclinical effects have been reported to occur at workplace air concentrations of ≥ 20 ug/m³
- Tolerable intake for elemental mercury vapor of 0.2 ug/m³, 24/7



Review of Additional Scientific Literature: Summaries of 34 Studies

Studies on Human Mercury Toxicokinetics and Exposure Characteristics

- Background levels of Hg in urine—no amalgams—
0.54-1.4 ug/g Creatinine (Cr)
- Persons with amalgams not occupationally exposed to mercury
range of $\leq 1-3$ ug/g Cr
- For each 10 Hg amalgam surfaces, urine levels increase by 0.8 – 1.4 ug/g Cr in adults, less in children

Human Mercury Toxicokinetics and Exposure Characteristics (cont.)

- Approximately 70-80% Hg is absorbed when inhaled
- Airborne levels of $<10 \text{ ug/m}^3$ are not accurately reflected in urine Hg levels
- Removal of Hg amalgam restorations (fillings) does not result in a large decrease in blood Hg levels, even 2-3 years after removal

Human Mercury Toxicokinetics and Exposure Characteristics (cont.)

- In utero (fetal) exposure to Hg--placental transfer--is greater than postnatal exposure with neonatal Hg levels decreasing after birth even with continued exposure via breast milk

Studies on Human Occupational Exposures to Mercury Vapor and Neurobehavioral Outcomes

- Occupational exposures to high levels
 - At concentrations of mercury vapor that exceed occupational exposure guidelines neuropsychological effects are the most sensitive endpoints
 - Workers exhibited neurological deficits at the end of chronic exposure (urine Hg values were ~21 ug/g Cr at time of testing) that improved when tested five years later

Occupational exposures to high levels (cont.)

- Workers occupationally exposed to very high levels (mean peak urine levels of >460 $\mu\text{g/g}$ Cr or more than ~ 100 - 200 times greater than those observed in persons with dental amalgams) have long-lasting effects on peripheral nervous system function, while most measures from an extensive neurobehavioral test battery showed no residual effects; no findings of effects on tests for dementia and cognitive function
- There was no association between occupational exposure to Hg and congenital malformations

Occupational exposures in dental professionals

- Chelation study suggests that the Hg body burden is greater than indicated by pre-chelation urinary Hg levels
- Neurobehavioral deficits reported
 - Finger tapping, hand steadiness, visual discrimination; correlated with measures of recent or current exposures
- However:
 - The neurobehavioral deficits reported are not shown in other occupationally-exposed groups where urine Hg levels were higher
 - No cohort comprised of non-dental controls
 - Lack of association between many outcomes and indices of long-term Hg exposures
 - Suggests that these effects may reflect confounding of Hg exposure with other occupational exposures, something that the study designs cannot rule out

Occupational exposures in dental professionals (cont.)

- Human Genetic Polymorphisms and Interactions with Urine Mercury Levels
 - Lack of correlation between indices of long-term mercury exposure and neurobehavioral outcomes
 - Only an effect of current mercury exposure (indicated by urine mercury levels at the time of testing)
 - Evaluated effects of genetic polymorphisms (BDNF; CPOX4) which appear to be associated with alterations in important behavioral responses (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, largely because of the shortcomings related to lack of control groups and other deficiencies

Studies of Human Amalgam Exposures

- Two new prospective clinical trials in children:
 - No adverse effects when followed for 5 or 7 years after amalgam placement.
 - Outcomes included extensive and repeated assessments of a multitude of neurobehavioral functions including IQs

Studies of Human Amalgam Exposures (cont.)

- Adult retrospective studies with large sample sizes: data do not support adverse effects from mercury amalgam
 - Association between Hg amalgams and increase in hazard ratio for Multiple Sclerosis
 - However, the number of observations was very small (7 out of 20,000) and the MS incidence in the study population was well below that of the general population (~29/20,000)
 - Trend for other responses was not in the direction showing adverse effect (kidney disorders, inflammatory responses and toxic neuropathy had lower relative risk)

Studies of Human Amalgam Exposures (cont.)

- Cross-sectional study in adults: no correlation between urine Hg levels and endpoints assessing several levels of the neuraxis
- One study showed significant correlations between number of amalgam surfaces and decreased vibrotactile response
 - The effect was demonstrable only in select groups
 - There were no urine Hg data, making interpretation and dose-response analysis difficult
- Studies that focused on low birth weight infants and persons with Alzheimer's disease found no evidence that Hg contributed to either condition

Animal Studies

- 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 high concentrations of mercury vapor during critical periods of gestation did not cause any significant adverse effects on electrophysiological outcomes in rat offspring when tested as adults
- While informative, the data from recent animal studies offered limited insights into the effects of mercury vapor at the levels experienced by persons with amalgams (animal exposures were $>1000 \text{ ug/m}^3$)

Overall Review Conclusions

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.