The US Dental Amalgam Debate, 2010 Meeting of the FDA Dental Products Panel

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Abstract: An overview is presented of the current scientific debate being conducted in the US regarding health concerns associated with the mercury in dental amalgam. Much of the information reviewed was presented at a meeting held on December 14 and 15, 2010 by the Dental Products Panel of the Medical Devices Advisory Committee of the Food and Drug Administration. The scientific and historic context of the debate is provided, followed by scientific arguments, public testimony, panel deliberation and amalgam policy outside the US.

Key Words: dental amalgam toxicity, amalgam, mercury, mercury toxicity

Introduction

The Food and Drug Administration (FDA) convened a meeting on December 14 and 15, 2010 to consider FDA policy regarding the safety of dental amalgam.[1-12] Dental amalgam, commonly called "silver filling" material, is composed of about 50% mercury mixed with other metals including silver, tin and copper. At the meeting, the FDA Dental Products Panel of the Medical Devices Advisory Committee considered whether a 2009 FDA rule[13] adequately addressed the health risks posed by the mercury contained in the fillings. The meeting included scientific and public testimony, as well as panel deliberation, providing a forum to present information pertinent to the dental amalgam debate.

The use of mercury in dental restorations has been debated since at least the early 19th century. Reviews are available by those who support[14-20] and oppose[21-25] the continued use of dental amalgam. A review supporting amalgam was published a few months before the 2010 FDA meeting[20] and a review opposing amalgam was published a month after the meeting.[25]

Mercury, from whatever source, is toxic at high exposure levels.[26,27] It is generally accepted that mercury escapes from amalgam fillings and enters the body of the bearer.[26,27] Mercury from amalgam also crosses the placenta into the developing fetus and is associated with increased mercury levels in breast milk.[26,27] Issues debated include how much mercury is released by amalgam fillings, how much enters the body, and how that amount compares with safe exposure levels for adults, children and developing fetuses.

The Toxicological Profile for Mercury[26] discusses several symptoms of mercury poisoning including: personality changes (irritability, shyness, nervousness), tremors, changes in vision, deafness, muscle incoordination, loss of sensation, memory difficulties, kidney problems, irritation in the mouth and lungs, damage to the stomach and intestines, nausea, vomiting, diarrhea, increases in blood pressure and heart rate, skin rashes, eye irritation, fertility problems, effects on the developing fetus including termination of pregnancy, autoimmune response, dizziness, joint pain, weakness, insomnia, numbness, tingling and reflex abnormalities. Whether *dental amalgam* is associated with these symptoms, however, is debated. It is also debated whether low-level mercury exposure in general and dental amalgam in particular is associated with numerous symptoms *not* found on the toxicological profile for mercury.

It is accepted that some people have adverse *acute* allergic reactions to mercury and perhaps the other metals in amalgam fillings.[26,28] These people have an immediate negative reaction, developing redness and lesions similar to a typical skin allergic reaction. The acute reaction is usually self-limiting and diminishes over time or is effectively mitigated by eliminating contact with the material. It is debated, however, whether the mercury from dental amalgam is a contributing factor to *chronic* mercury toxicity, an illness that has similar symptoms to high level mercury toxicity but may take several months, years or even decades to develop. The association of the mercury *from amalgam* with specific diseases such as multiple sclerosis, autism, Parkinson's disease and Alzheimer's disease is also debated as is any association with poorly understood conditions such as fibromyalgia and chronic fatigue syndrome.

The main participants in the scientific debate in the United States are the American Dental Association (ADA) and the International Academy of Oral Medicine and Toxicology (IAOMT). The ADA is the primary professional dental organization in the United States and is comprised of over 157,000 member dentists and hundreds of affiliated state and local chapters. The ADA was founded in 1859, in part to promote and standardize the use of dental amalgam, but historic and current technical interest extends to all aspects of dentistry and includes the ADA Seal of Acceptance Program which evaluates the safety and efficacy of dental products.

According to a 2009 statement by the ADA, "Dental amalgam is considered a safe, affordable and durable material that has been used to restore the teeth of more than 100 million Americans. It contains a mixture of metals such as silver, copper and tin, in addition to mercury, which binds these components into a hard, stable and safe substance. Dental amalgam has been studied and reviewed extensively, and has established a record of safety and effectiveness." [28]

The IAOMT is a professional scientific organization comprised of over 700 members and over a dozen international chapters. Most members are dentists but physicians and researchers from related scientific fields are also included. The IAOMT was founded in the 1984 to *scientifically* address health and safety concerns regarding the mercury in dental amalgam. Since its

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inception, the IAOMT has funded primary research in the realm of oral medicine and toxicology and the development of techniques to reduce mercury exposure to dental personnel and patients. The IAOMT currently provides an Accreditation Program for dentists wishing to learn biocompatible dental techniques including methods to reduce mercury exposure during amalgam removal.

According to a 2009 position paper by the IAOMT, "Chronic exposure to mercury, even in minute amounts, is known to be toxic and poses significant risks to human health. Current scientific evidence clearly demonstrates that dental amalgam unnecessarily exposes dental patients to substantial amounts of mercury vapor, particulates and other forms and is therefore not a suitable material for dental restorations."[29]

The small number of IAOMT dentists compared with the ADA is not indicative of the number of dentists who no longer use dental amalgam. A 2005 survey of 714 members of the Academy of General Dentistry revealed that more than 30 percent considered their practices to be "amalgam-free."[30] Recent surveys by a dental marketing company, The Wealthy Dentist, found dentists split nearly 50/50 regarding the use of amalgam[31] but only 25% favor banning the material.[32]

Comments collected during the surveys conducted by The Wealthy Dentist reveal dentists hold passionate and diverse views regarding dental amalgam. Those who continue to use amalgam mention its lower cost, greater durability and better suitability for certain types of restorations especially when moisture is a concern. Dentists concerned about the toxicity of mercury claim modern materials and techniques have made the material obsolete; some have practiced for decades without placing an amalgam restoration. Other dentists have discontinued or greatly reduced the use of amalgam, not for safety concerns, but because of the tendency of amalgam to fracture teeth or because of patient's preference for materials that better match the natural color of teeth. The debate is not new; controversy regarding the mercury in dental amalgam has existed since before the US civil war.

Declining Use of Mercury

Mercury has been in use medicinally and commercially for thousands of years but there is also a long history of concern related to its toxicity.[33] Paracelsus discussed mercury's medicinal uses and toxic properties in the 16th century.[33] Mercuric nitrate solutions, used for stiffening felt, caused the slurred speech, hallucinations, irritability, depression and tremors experienced by hat makers from the 17th to 19th centuries.[33] Mad hatters disease may have been the basis for the name of the Lewis Carroll character in *Alice's Adventure in Wonderland*. Mercurous chloride, Hg_2Cl_2, also known as calomel, is a mercury salt that was used in medicine, cosmetics and teething powder. Calomel teething powder was used through the 1950s until it was suspected and later verified as causing widespread mercury poisoning in the form of acrodynia (pinks disease).[33] A similar compound, mercuric chloride, $HgCl_2$, was used historically to treat syphilis. Another salt, mercury iodide, Hg_2I_2, was a common over the counter medicine called protiodide used in the 19th century to treat several illnesses including kidney disease, acne and syphilis. Because of their toxicity and the availability of superior treatments, including antibiotics, these mercury compounds are no longer used medicinally and it is illegal in many countries, including the US, to use calomel in cosmetics.

The use of mercury compounds as cosmetic ingredients is currently limited by the FDA to eye area cosmetics such as mascara.[34] Minnesota has taken a tougher stance, banning mercury as an ingredient in all cosmetics sold in the state since January 1, 2008.[35] Minnesota's mercury ban also includes over-the-counter pharmaceuticals, toiletries, fragrances, stoves, barometers and cooking thermometers. The use of liquid mercury in thermometers, manometers (for blood pressure measurement) and similar devices has been greatly reduced because of the hazard associated with spilled mercury in the event of accidental breakage as well as concern when the devices are disposed. Methylmercury, consumed when eating certain types of fish, has led to FDA and EPA advisories for pregnant women, women who might become pregnant, nursing mothers and young children.[36]

Ethylmercury based thimerosal (ethylmercurythiosalicylate sodium salt) has largely been discontinued as a topical antiseptic but is still found in some products including mascara (except in Minnesota). Thimerosal is also used as a preservative in some medical injections, including several influenza vaccines and immunoglobulin injections including those given to children. The safety of vaccines in general and thimerosal containing vaccines in particular is currently debated especially for injections given to pregnant women and children. Significant scientific gaps exist; for example, many regulatory guidelines are based on epidemiological and laboratory studies of methylmercury while thimerosal is based on ethylmercury.[37] The FDA currently promotes the reduction of mercury in vaccines as a *precautionary* measure.[37] Thimerosal is no longer used as a preservative in *routine* childhood vaccinations given in the US, the European Union and a few other countries. Manufactures have recently responded to consumer concern by increasing the availability of mercury-free flu vaccines.

History of the Amalgam Debate

IAOMT dentist David Kennedy presented an overview of the history of dental amalgam at the FDA panel meeting.[1] Published overviews of the history by dentists holding the IAOMT view[22] and the ADA view[38] are also available. The use of silver colored pastes to restore teeth, some of which are known to have contained mercury, extends back hundreds of years in China and Europe. Modern dental amalgam was developed in Paris in 1818 by Louis Nicolas Regnart who developed an amalgam formulation that, unlike predecessors, did not require heating.[38] Dental amalgam was introduced to North America in 1833 by the Crawcour brothers who called the material royal mineral succedaneum.[22,38] The deceptive promotion of amalgam and unprofessional practice of the Crawcour brothers, who allegedly packed in the material without removing the decay,[38] is viewed, historically and contemporarily, with disdain by dentist both supportive and opposed to the use of amalgam.[1,38,39]

Controversy because of the mercury content in amalgam began in at least 1840 in the US and earlier in Europe.[38] In 1845, the American Society of Dental Surgeons, the prominent dental professional organization at the time, made members sign a pledge not to use amalgam, considering its use malpractice.[22,38,39] The primary restoration materials at the time were gold and tin. Gold, however, was expensive and both materials were difficult to apply compared with amalgam. As amalgam formulations and techniques gradually improved, the popularity of amalgam increased and the number of dentists

who refused to use the material declined. The American Society of Dental Surgeons, however, continued to oppose amalgam which resulted in bitter debate as well as the expulsion and resignation of many members until the unanimous repeal of its pledge against amalgam in 1850.[39] Despite the repeal, the Society never recovered from the bitter debate and the organization disbanded in 1856.[22,38,39]

The ADA was founded in 1859 to replace the disbanded Society and to promote and standardize the use of dental amalgam. During most of the 19th century, a multitude of amalgam formulations and techniques resulted in numerous fractured teeth and failed restorations. Numerous cases of injury associated with amalgam, including cases of mercury poisoning, resulted in continued opposition to the material.[38,39] Proponents, however, claimed it could be safe and effective as long as proper formulations and techniques were employed.[38]

In the 1880s, E. S. Talbot addressed the amalgam mercury debate, describing the discussion as causing "bitterness and enmity" among dentists.[39] Talbot was also concerned with the limited scientific data available to address the debate. Talbot produced some of the earliest scientific investigation into the mercury safety issue including publishing evidence that mercury was released by dental amalgam.[39] Talbot also cited several cases of illness that were attributed to amalgam based mercury poisoning.[40] Talbot's concerns were largely ignored. Research efforts were directed to reduce variation in amalgam composition and placement techniques. In 1895, dental amalgam manufacturer and restoration techniques were standardized by Chicago dentist Greene Vardiman Black.[38] Black's work greatly reduced the tendency of amalgam to fracture teeth enhancing the popularity of the material.

Concerns regarding mercury vapor in general and amalgam specifically were raised in several papers written in the 1920's and 1930s by German chemist Alfred Stock.[41,42] Stock described his personal battle with occupationally induced mercury poisoning and possible exacerbation by his amalgam fillings. Stock's work resulted in significant investigation into the amalgam issue in Germany during the 1930s but concern dissipated during World War II. For the consumer, the primary alternative to amalgam was gold.

Mercury-free composite materials were first introduced in the late 1940s when processes were developed to bond acrylic resins to teeth pretreated with acid etchants.[43] Composite resin materials and processes were improved in subsequent decades and materials became available that offered a better match to the natural color of teeth. The durability of composites, however, remained inferior to amalgam.

A 1957 study of mercury in amalgam involved giving eight volunteers four new fillings each, labeled with radioactive mercury.[44] The author was able to detect excretion of the radioactive mercury in urine for seven days and in feces for thirteen days, but concluded that the release of mercury from the fillings, while not zero, was self-limiting and not a problem for the bearer. The consensus among most dentists was mercury was released during the setting phase, but once the amalgam set, the mercury was tightly bound and not released into the body of the bearer.

Mercury containing amalgam and mercury-free alternatives underwent significant reformulation in the 1960s and 1970s.[45] In 1962, Innes and Youdelis introduced high-copper amalgam being the first major change since Black's 1895 formulation.[46] Multiple high-copper amalgam formulations were developed in the 1970s and 1980s gaining popularity because of superior mechanical and corrosive properties compared with the low-copper predecessor.[38,45] More rigid composite resins based on bis-GMA were also introduced in the early 1960s.[43] Light cured dental composites were first introduced in 1972[43] as were glass-ionomer cements.[47,48] In 1974, composite resins based on urethane dimethacrylate (UDMA) were introduced.[43] Modern dental restoration materials, both amalgam and mercury-free, are based largely on the formulations introduced in the 1960s and 1970s.

Research addressing dental amalgam mercury concerns increased dramatically starting in the 1970s. Searching "Dental Mercury" on PubMed.gov results in over 2600 references dating back to the 1940s with over 2500 published since 1970 (Figure 1). Research in the 1960s and 70s was largely concerned with creating a mercury-safe environment for dental personnel. However, as new amalgam formulations were developed, there was concern regarding the mercury exposure to the bearer, especially during the setting phase.[49]

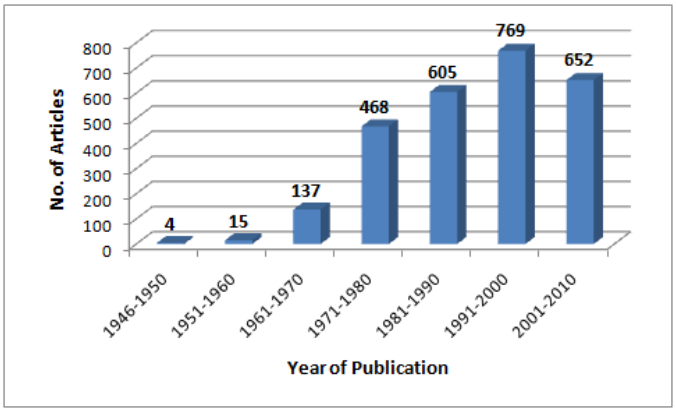

Figure 1 Results of PubMed.gov search for "Dental Mercury" shows the large number of articles published since 1970. One irrelevant reference from 1941 was removed from the results.

In the 1970s, dentists Hal Huggins began a vocal campaign against dental amalgam publishing a popular book on the subject with his wife in 1985.[50] Huggins still supports replacing amalgam restorations with mercury-free alternatives to alleviate certain health problems despite having his dental license revoked in 1996. The debate was further ignited in the late 1970s and early 1980s when several studies produced evidence that mercury vapor escapes from *set* dental amalgam even many years after placement.[51,52,53,54]

The evidence that mercury was released from set amalgam encouraged several dentists to join the anti-amalgam camp some making anecdotal claims of patients experiencing health improvement following replacement of amalgam fillings. Amalgam supporters countered that the amount of mercury released from amalgam was below toxic levels and characterized some of the amalgam opponents as unscientific, money-driven charlatans. In 1986, Consumer Reports published an article titled, *The mercury scare: if a dentist wants to remove your fillings because they contain mercury, watch your wallet.*[55] Scientific data to address the debate, however, was limited.

The IAOMT was founded 1984 to *scientifically* address health and safety concerns regarding the mercury in dental amalgam. IAOMT funded studies conducted on sheep[56] and monkeys[57], first published in 1989, showed mercury from amalgam accumulated in the organs and tissues of the bearer (Figure 2). The sheep studies were included in an exposé on dental amalgam that 60 Minutes aired on December 16, 1990 increasing public concern.

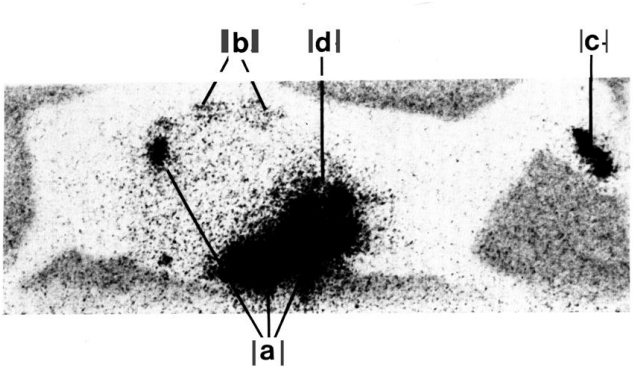

Figure 2 Full body scan of a sheep 29 days after placement of 12 occlusal amalgams labeled with 203Hg. The fillings were removed prior to the scan. (a) digestive tract. (b) kidneys. (c) gums and alveolar bone. (d) liver, partially obscured by the digestive tract (*Courtesy of the Journal of the Federation of American Societies for Experimental Biology*).[56]

In 1991, a review published in the Journal of the American Dental Association[14] and additional popular articles in Consumer Reports[58,59] argued that the levels of mercury released were safe and that the replacement of dental amalgam to address health concerns was unwarranted. A 1995 review by IAOMT members challenged the ADA opinion.[21] Rod Mackert, the author of the 1991 ADA review, and Anne Summers, a co-author of the 1995 IAOMT review, both presented at the 2010 FDA meeting.

The cost, safety and effectiveness of mercury-free materials are an important aspect of the dental amalgam debate. There are currently three primary mercury-free alternatives to dental amalgam: gold, glass-ionomer cements and composite resins. Gold remains a durable option but is expensive compared with amalgam and does not match tooth color. Glass-ionomer cements are limited to use in small restorations and do not match tooth color as well as composite resins. In the 1990s and 2000s the durability of composite resins were greatly improved with some being marketed as amalgam alternatives suitable for large restorations.[43,60,61] The mercury-free alternatives, however, are not without safety concerns. Bis-GMA based composite materials contain Bisphenol A, a known endocrine disrupter that may contribute to the development of breast cancer. Mercury-free materials and techniques continue to be refined and developed impacting the amalgam debate.

The amalgam debate has waxed and waned for almost 200 years. The modern debate, however, is based largely on studies published since 1970. FDA regulatory authority of dental amalgam began in 1976, just as the modern amalgam debate was emerging.

FDA Regulatory History of Amalgam

During the 2010 FDA meeting, Michael Adjodha, engineer and reviewer in FDA's Dental Devices Branch, provided some background information on the FDA's regulation of dental amalgam.[1] The use of dental amalgam predates the FDA and was grandfathered in when FDA regulatory authority was extended to medical devices in 1976. The FDA classifies medical devices according to assessed risk. Class I is used for lowest risk devices and requires only *general* safety controls; Class II is for moderate risk devices and requires *special* controls; and Class III, is for highest risk devices and requires manufactures to provide extensive *proof of safety* and formal FDA premarket approval.

Dental amalgam is formed from two components, in approximately equal parts, of liquid mercury and a metallic alloy powder consisting primarily of silver, copper and tin. The two components are mixed, forming a putty that sets and hardens as it is used for dental work. For many decades the two components were marketed separately and mixed at the dental office. Modern amalgam materials are sold in capsules with the two components separated by a septum. The capsules are placed in an *amalgamator*, which combines the two components and agitates the capsule mixing the amalgam.

In 1987, the two components were classified separately, the mercury as Class I and dental alloy as Class II. Michael Adjodha explained the mixed form was not classified, since the two components were traditionally marketed separately.[1] The 1987 rule was considered inadequate by some especially after the evidence from the sheep studies was published.[56] Beginning in 1990, several citizens' petitions were filed requesting the FDA to take action regarding amalgam including petitions to ban the material or classifying it as a Class III device.

In 1993, the Department of Health and Human Services (HHS) conducted a multi-agency literature review concluding amalgam does not pose a serious health risk to the general public. Dental amalgam was the subject of several FDA Advisory Committee meetings held in 1993 and 1994, when the Dental Products Panel recommended the FDA classify amalgam as a Class II device. The 1993 review was updated by HHS in 1995 and 1997 again concluding that the body of literature through 1997 does not support claims of adverse health effects from amalgam, except for rare allergic or hypersensitive reactions.

In 2004, a National Institutes of Health (NIH) and FDA funded literature review concluded there was insufficient evidence to support a relationship between exposure to dental amalgam and kidney or cognitive dysfunction, neural degenerative disease, autoimmune disease, or adverse pregnancy outcomes. In 2006, the FDA prepared a draft White Paper concluding dental amalgam is not associated with adverse health effects in populations aged six and older.[62] Later in 2006, a joint meeting of the Dental Products Panel and the Peripheral and Central Nervous System Drugs Advisory Committee was convened to consider the scientific merit of the 2006 White Paper.

The 2006 panel took two votes addressing the questions, "Does the FDA draft White Paper objectively and clearly present the current state of knowledge about the exposure and health effects related to dental amalgam?" and "Given the amount and quality of information available for the draft FDA White Paper, are the conclusions reasonable?"[63]

The panel answered "NO", voting 13 to 7 against the white paper on both questions. A majority of both the dental and

drugs subpanels rejected the white paper. Some individuals voted YES on one question and NO on the other.

According to the 2006 meeting summary, "Those voting no expressed concern that the paper contained too many research gaps and implied a safety that was not really known. Those voting yes recognized deficiencies but felt the conclusions were reasonable for the available data."[63]

Responding to the committees concerns, the FDA updated the 2006 White Paper in 2009 adding an Addendum.[64] On July 28, 2009, the FDA issued a final rule that classified dental amalgam as a Class II (moderate risk) device. The rule also reclassified *mercury* from a Class I (least risk) to a Class II (more risk) and designated a special controls guidance document for dental amalgam.[13]

The FDA's summary of the 2009 rule[13] is currently available on the FDA website and is included in the back of this document. The summary includes the FDA's guidance language, which was a focal point of the dental products panel meeting. Quoted text from the FDA document is shown in blue throughout this paper. Numbers used to reference endnotes were modified to conform to this document.

The FDA guidance document recommends disclosure of the mercury content and language stating "dental amalgam releases low levels of mercury vapor, a chemical that at high exposure levels is well-documented to cause neurological and renal adverse health effects." [13]

FDA guideline also notes that "clinical studies have not established a causal link between dental amalgam and adverse health effects in adults and children age six and older. In addition, two clinical trials in children aged six and older did not find neurological or renal injury associated with amalgam use[65,66,67,68,69] ." [13]

2010 FDA Dental Products Panel Meeting

Four petitions were made to the FDA to reconsider the 2009 rule. James Turner, Richard Edlich, James Love and Robert Reeves were among the attorneys filling petitions (Love and Reeves filed two petitions jointly).[3,4] Citizens for Health, NoMercury and Moms Against Mercury, along with many individual signers, supported the petitions and presented testimony at the hearing. Consumers for Dental Choice, led by attorney Charles Brown, and Dental Amalgam Mercury Solutions, represented by Carol Ward and Marie Flowers, also participated in the meeting. The IAOMT assisted in drafting the petitions filed by Love and Reeves, and presented the scientific case against amalgam.[70]

The petitioners believed that important scientific results were not properly considered by the FDA in making its 2009 determination, arguing the "FDA underestimated the level of exposure to mercury from dental amalgam and failed to adequately consider differences among different age groups that could affect absorbed dose."[5]

The petitioners argued the FDA should either ban and recall amalgam or place restrictions on its use especially for pregnant women, children under six, and sensitive individuals.[3,4] Some of the petitioners also argued that dental amalgam, if not banned entirely, should be reclassified as a Class III (highest risk) device[1,2,3] which would require manufactures to provide extensive proof of safety and formal FDA approval.

The FDA Dental Products Panel at the December 2010 meeting comprised 22 members[6] charged with developing consensus statements and considered scientific opinion for consideration by FDA policy makers. Ten of the panel members, including Panel Chair Marjorie Jeffcoat, are accomplished dentists and dental scientists including: faculty members or deans of dental schools; experts in dental materials; and authors and editors of peer-reviewed publications and dental books. One of the panel dentists, Michael Fleming, is an IAOMT member while others are known advocates of the ADA position.

Among the other panel members, eight have scientific or medical credentials in the areas of toxicology, epidemiology, or pediatric neurology. Michael Bates was principle investigator of a large epidemiological study supporting the view that dental amalgam is safe.[71] Janine Janosky is an expert in biostatistics and has worked with panel member and IAOMT dentist Michael Fleming to address the economic implications of banning dental amalgam. Thomas Burbacher is an expert on methylmercury toxicology and signed the IAOMT position paper opposing the use of dental amalgam.[29] William O'Brien is a metallurgical engineer who has studied the release of mercury from dental amalgam. Michael Dourson and Susan Griffin are toxicologists who work on the development of toxicity values with Dourson having worked specifically on the toxicity value for mercury. Judith Zelikoff is an expert on environmental medicine and inhalation toxicology especially metals. Suresh Kotagal is a pediatric neurologist from the Mayo Clinic. The remaining four members of the panel included an Industry Representative, a Consumer Representative a Patient Representative and a Federal Officer from the FDA charged with managing meeting details.

A complete list of members, and their areas of expertise, is provided at the end of this document. The FDA roster includes additional biographical information and lists the regular panel members as voting and the temporary members as non-voting.[6] Unlike the 2006 meeting, however, no votes were taken. The FDA would consider the collected comments of the entire committee as well as the presenters.

Four guest speakers, experts in toxicology, pharmacology and risk assessment, also served the panel but did not participate in committee deliberations. Three of the speakers were charged with answering "Homework Questions"[7,8,9,10] designed to assist the panel. The fourth guest speaker reviewed the presentations and literature submitted to the panel providing focus to the many issues raised. Anthony Watson, Director, Division of Anesthesiology, General Hospital, Infection Control, and Dental Devices at the FDA, led several FDA representatives charged with clarifying the questions for the panel.[5]

The FDA asked the panel to address three sets of scientific questions designed to critically consider the arguments raised by the petitioners. The first set concerned the level of exposure to mercury that amalgam bearers receive from their dental amalgams. The second set concerned how the Reference Exposure Level (REL) for elemental mercury – or the level considered protective assuming chronic exposure of the general population and vulnerable subpopulations – should be

determined. The third set concerned clinical studies of exposure to dental amalgam.[2,5,7]

Amalgam Debate: Science & Rhetoric

The passion fueling the amalgam debate has led members of both the IAOMT and the ADA to make statements with more rhetorical than scientific merit. These statements are usually an attempt to simplify complicated issues and to persuade the general public. Two commonly touted statements, one from each side of the debate, will be considered to illustrate the situation. Analysis of the two statements will also provide an opportunity to review fundamental chemistry before presenting a chemical description of amalgam, a complex material. The statements were repeated at the 2010 FDA panel meeting by leaders from the IAOMT and ADA.

Is Mercury the Most Toxic Non-radioactive Element?

During the public presentation at the FDA meeting John Kall, reading a statement by IAOMT President Matthew Young, repeated a claim often made by those opposing dental amalgam that mercury "is the most toxic nonradioactive element on earth."[1]

Less technical opponents of dental amalgam unintentionally substitute the word "substance" for the word "element" making the statement unequivocally false. There are many non-radioactive *substances* that are much more toxic than mercury. As is, the statement exaggerates the toxicity of mercury by only comparing elemental mercury with other non-radioactive elements.

Elements are the fundamental building blocks of all chemicals and are conveniently classified on the periodic table. As of 2011, there are 118 chemical elements but only 94 are found naturally on Earth; the others have been produced in particle accelerators. Among the 94 naturally occurring elements, 80 are non-radioactive (bismuth, with a half-life longer than the age of the universe is currently considered radioactive). Describing mercury as the most toxic non-radioactive element limits the comparison to only 79 other elements and limits the type of mercury considered to its elemental metallic form.

How does mercury compare with the other 79 non-radioactive elements? Mercury is the only metal element that is liquid at room temperature and standard atmospheric pressure. Metallic mercury can contact the skin with little harm (although this is not recommended).[26] Elemental mercury also has low toxicity when ingested as less than 0.01% enters the body of a healthy person through the stomach or intestines.[26] Ingestion of half a teaspoon (about 204 g) of liquid mercury with little toxic effect has been reported.[26] Arsenic is more toxic than mercury when ingested and iodine, an element essential to life, can be lethal if 2 g are ingested.[72] Sodium metal, because of its violent reactivity with water, will explode or burst into flames if ingested. Mercury is not very toxic when ingested.

The IAOMT, however, is not considering *ingested* mercury when claiming it to be the most toxic non-radioactive element but rather inhaled mercury vapor. About 80% of inhaled toxic mercury vapor is absorbed by the lungs and enters the bloodstream.[26] The IAOMT, however, does not indicate the method used to compare the toxicity of mercury vapor with other chemical elements. Are acute, intermediate or chronic effects compared? Are lethal doses considered? Are values corrected for differences in molecular weight? Are the number and degree of effects, bioaccumulation or environmental prevalence considered?

The permissible exposure limit (PEL) provides a method of comparing relative toxicities of vapors. The PEL is the maximum level of exposure permitted in occupational settings; more toxic substances should have lower PELs. Occupational Safety and Health Administration (OSHA) sets the PEL for mercury vapor at 0.1 mg/m^3 (milligrams per cubic meter).[73] The PEL for mercury, while lower than arsenic or cadmium, is higher than lead and beryllium.[73] Mercury is *not* the most toxic nonradioactive element based on PEL. The unique properties of each chemical element also complicate comparisons of toxicity. Mercury has a lower PEL than chlorine gas but both can be extremely harmful in similar concentrations (40 mg/m^3).[73,74] Because of mercury's low vapor pressure (tendency to go from liquid to gas), typical room ventilation is sufficient to prevent conditions in which mercury vapor is lethal. Chlorine gas, however, was used in chemical warfare during World War I.[74] Ranking toxicity based on PEL demonstrates the difficulty in finding an acceptable method of comparing the toxicity of chemical vapors.

The IAOMT claim of mercury's high relative toxicity may have its origin in a studies reported in 2001[75] showing the destructive effects of small amounts of mercury on the membranes of neurons isolated from snails. Aluminum, lead, cadmium and manganese, in similar concentrations, were found to be less destructive than mercury. A recent review, repeating the IAOMT claim,[25] lists six reasons supporting mercury's high comparative toxicity including: mercury vapors unique volatility compared with other metals; the ability of mercury to penetrate into tissues; the affinity of mercury to thiol groups (biological compounds containing sulfur) inhibiting biological activity; and the difficulty for natural and pharmaceutical agents to remove mercury especially from nervous tissues. Arguments can be made justifying mercury's high toxicity. However, it is difficult to compare mercury to other toxic elements that may behave very differently.

The claim that mercury is the most toxic non-radioactive element requires significant qualification regarding how the comparison is made and has strong potential to be misleading.

Is Dental Amalgam Analogous to Salt?

Proponents of dental amalgam argue that mercury in dental amalgam is bound in such a way as to render it safe. An often made analogy between dental amalgam and table salt was repeated during the public presentations at the FDA meeting by Dr. Dennis Charlton, president-elect of the Pennsylvania Dental Association (a constituency of the ADA).

> The mercury in silver-colored restorations is bound in a molecular form in much the same manner as elemental chlorine gas is bound in the molecule of sodium chloride. And I'm sure most of you realize sodium chloride is simple table salt and that chlorine gas is poisonous. The molecule, the molecular combination of sodium and chloride makes it safe to be used in cooking and as a table spice.[1]

One problem with the statement is amalgam and salt have very different chemical descriptions. Sodium chloride (table salt) is a compound while amalgam is a mixture. Elements are the

fundamental building blocks of chemistry and can be combined chemically to form an essentially unlimited number of molecules.[76] Molecules formed from at least two *different* elements are called compounds. Elements and compounds can be combined, non-chemically, to form an even larger number of mixtures. Solutions, suspensions, colloids and alloys are types of mixtures. Compounds tend to be more tightly bound than mixtures and usually maintain stoichiometry; the relative proportion of each element is fixed. Table salt is always 50% sodium and 50% chlorine and forms an ionic crystalline solid. Amalgam is better compared with *salt water* since both are mixtures. Any amount of salt may be mixed with water until the solution saturates. Similarly, you can have varying amounts of mercury in amalgam. It is misleading to compare amalgam, a mixture, with a compound like salt.

The table salt analogy also suffers from the implied assumption that if toxic elements are combined chemically they become nontoxic. Some toxic elements, like sodium and chlorine, can be combined to create nontoxic compounds. Similarly, mercury sulfide, because of its low solubility, is not very toxic. Combining elements into compounds, however, does not always render them safe. Some salts, including many mercury salts, are toxic. Organic (carbon containing) compounds, like methylmercury, found in some seafood, and ethylmercury, used as a germicide, are toxic. Unlike metallic mercury, some forms of organic mercury can be toxic when ingested or when coming in contact with the skin. 95% of toxic methylmercury is absorbed when ingested.[12] A few drops of dimethylmercury, $Hg(CH_3)_2$, penetrated a protective glove contacting the skin and ending the life of Karen Wetterhahn, Professor of Chemistry at Dartmouth College. Conversely, nontoxic elements can be combined to form toxic compounds. Nontoxic carbon and oxygen can be combined to create toxic carbon monoxide (CO) or nontoxic carbon dioxide (CO_2). One cannot draw a conclusion regarding the toxicity of a substance based on the existence of chemical bonds or by analogy with another substance.

There has been a tremendous amount of scientific work bearing on the amalgam controversy. Both sides of the debate have a responsibility to carefully consider the scientific merit of their claims and arguments, as well as the potential for a statement to be misleading, and not allow passion and attempts to simplify complicated issues to distort the science. The reader new to the debate is cautioned that the distorting effects of agenda and emotion often unintentionally extend into the peer reviewed literature and other articles on the subject. This overview is not an exception.

Chemical Description of Amalgam

Amalgam is typically defined as being an *alloy* containing mercury and other metals. Alloys are *mixtures* of elements and compounds, typically metals, forming a metallic matrix (stainless steel is an alloy). Dental amalgam is a mixture of elemental mercury and mercury compounds as well as other metals and metal compounds. Chemical reactions occur when amalgam is mixed (a process called trituration) creating chemical bonds between the mercury and other metals called intermetallic compounds. Dental amalgam consists of regions containing different intermetallic compounds called phases. Because of the inability of the various phases to mix, dental amalgam is sometimes classified as a solid *emulsion* (a mixture of olive oil and vinegar is an emulsion). The mercury in dental amalgam is not necessarily completely bound within the matrix. Alloys, like bronze and steel, have physical, mechanical and corrosion properties that are tailored by composition and fabrication processes. Similarly, the properties and relative stability of dental amalgam, the amount of mercury released and the release mechanisms, as vapor, particulate or through corrosion, can depend on composition and fabrication techniques.

In 1895 the alloy composition of amalgam was standardized by G. V. Black[38] to what is called gamma-2-phase amalgam formed by mixing about 50% liquid mercury with a powder containing 60% silver, 29% tin, 6% or less copper and 2% or less zinc.[45] The material is effective for dental restoration but develops intermetallic phase regions including silver-tin gamma regions, silver-mercury gamma-1 regions and tin-mercury gamma-2 regions. The difference in electrochemical potential between the regions results in crevice corrosion with the soft gamma-2 phase corroding the fastest.[77]

In 1962, a new composition was developed by Innes and Youdelis where the metallic contains significantly more copper (12% to 30%).[46] The gamma-2 phase tin-mercury regions are replaced by the formation of tin-copper regions. The reduced-gamma-2-phase or “high copper” amalgams are less expensive and have better corrosion and mechanical properties than the low-copper predecessor.[77]

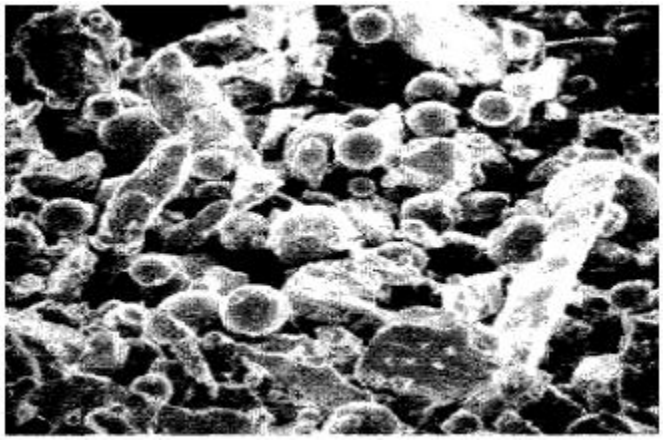

Figure 3 The scanning electron micrograph of admixed amalgam shows both spherical and lathe-cut shaped particles. Formulations are also available that contain only lathe-cut or only spherical particles.[78]

The alloy composition for high-copper amalgam depends on the manufacturer with silver ranging from 40% to 70%, tin 12% to 30% and copper, like tin, from 12% to 30% in the powder.[45] Depending on the formulation, the amount or mercury used can also vary from about 40% to 50%. Some manufacturers also add smaller amounts of indium, zinc and/or palladium. Zinc prevents oxidation of the other metals which keeps the alloy from turning dark.[45] Zinc-free amalgam is also available and reduces secondary expansion in amalgam contaminated by moisture.[45,78] Palladium reduces tarnish and improves mechanical properties.[45,78] Indium increases strength[45] and also effects the amount of mercury released from amalgam.[45,78] Depending on the manufacturing process, amalgam products can have lathe-cut particles, spherical shaped particles or mixtures of the two (Figure 3).[78]

Mercury Release from Amalgam

Variations in composition can change the amount of mercury released from amalgam. Palladium can decrease the amount of mercury released.[79] Indium is typically added in concentration of 4% or less to increase strength and reduce plastic deformation. Higher concentrations of Indium, 8% or more, added to *experimental* amalgam, has been shown to reduce mercury vapor release especially during the setting phase.[80,81] Less mercury is also required for mixing amalgam when it contains indium in concentrations up to 10%.[82] One explanation for the decreased release is the formation of indium oxide and tin oxide films which from a stable barrier in laboratory conditions.[83]

The amount of mercury released can depend on how the amalgam is formed. Once the amalgam is mixed and set, the restoration contains 41% to 51% mercury by weight.[84] The amount of mercury can depend on how, and for how long, the amalgam is mixed and the amount of delay between mixing and setting of the restoration.[45,77] The amount of mercury required to create a restoration also depends on the size and shape of the metallic particles in the powder which differ among manufacturing techniques[45,78] Spherical particles, for example, are easier to wet and require less mercury than lathe-cut particles.[45] Depending on the composition, amalgam can expand or contract slightly during the approximately 24 hours it takes to achieve its maximum strength. During this time, the dental patient is exposed to increased amounts of mercury vapor that decreases as the amalgam sets.[80,85]

This effect is mentioned in the FDA guidance language which includes "Mercury vapor concentrations are highest immediately after placement and removal of dental amalgam but decline thereafter."[13]

The amount of mercury released from dental amalgam can depend on its environment. The amount increases during chewing or when drinking hot liquids.[86,87] One study found that acidic environments, designed to mimic saliva, increased the amount of mercury released.[88] The same study found that high- and low-copper amalgam released similar amounts of mercury in neutral pH environments but high-copper amalgam released significantly more mercury in acidic environments.

Placing amalgam in contact with other dental materials like gold or metallic braces also increases the amount of mercury released. One study, conducted in artificial saliva solution, considered the effect of different amalgam alloys exposed to externally induced corrosion by galvanic contact with dental casting gold.[89] The study found no significant difference in the total mercury released between the conventional and high-copper amalgams as groups, but one individual product containing indium released significantly more mercury vapor than the two products with the lowest release. Another alloy composition study found the amount of mercury released following abrasion differed by over two orders of magnitude with high mercury release correlating strongly with decreasing amounts of tin.[90] The combined effects of environment and composition on the amount of mercury released from dental amalgam are complicated.

Boyd Haley, Professor Emeritus of Chemistry and Biochemistry at the University of Kentucky, has published mercury release estimates of amalgam under controlled conditions.[91] The results are available on the IAOMT website[92] and were presented by Haley to the FDA panel during the December meeting.[1] Amalgam restoration material was placed in Plexiglass® molds by nine different dentists, each using amalgam from one of three different manufacturers. The molds were sent to Haley's lab, where the amalgam was removed from the molds and allowed to set for three months to allow the mercury emission to stabilize. The amount of mercury released during the initial stabilization period was beyond the scale of Haley's test equipment.[1]

The amalgams remained in distilled water, at room temperature during the 25 day experiment. The water was gently mixed, without disturbing the amalgam, to allow the collection of 1 ml of water for analysis. The amount of measured mercury released ranged from 4.5 to 21 micrograms (µg) of mercury per day, per cm^2 surface area depending largely on the specific restoration tested as opposed to the day of water sample collection. Haley also found that brushing the amalgam led to a 5 to 10 fold increase in the amount of mercury released.

Haley's data were collected under controlled and artificial conditions that could underestimate or overestimate the levels of amalgam released in actual use. Haley reports that the set amalgams were removed from the molds and placed in water which differs from the air, saliva and tooth structure surrounding an actual filling. In Haley's test procedure, the surface area of *exposed* amalgam would be larger than a typical single restoration increasing the amount of mercury released. However, the amalgam remained at room temperature and was relatively undisturbed reducing the amount of mercury released. The data collection period was also limited, making it difficult to extrapolate over the lifetime of a filling.

What was compelling about Haley's data, however, was that even under rather controlled conditions, variations of more than a factor of four were observed depending on *both* the amalgam manufacturer and the dentist who placed the filling with no obvious trend. Some individual dentists showed high variation even though they were using amalgam from the same manufacturer. The data show little dependence on the day of sample collection indicating the variation between restorations is *not* due to experimental uncertainty or time dependence.

Haley's data and other peer reviewed studies suggest large differences in mercury release depending on the amalgam composition, manufacturing process, dental techniques, oral environment and habits of the amalgam bearer. How much released mercury from amalgam actually enters the body of the bearer?

Mercury Exposure from Amalgam

Exposure to mercury is predominantly via the lung, as mercury vapor, with reported absorption ranging from 61% to 86%.[11] Secondary routes of exposure include the gastrointestinal tract and the tissues in proximity to the amalgam. The amount of amalgam-related mercury exposure and bio-accumulation has been estimated using a variety of techniques.[19,22]

One method used to estimate the amount of amalgam-related mercury exposure is direct measurement of mercury vapor in the oral cavity using a meter. Jerome® Mercury Vapor Analyzers, which is typically used to monitor environmental air quality, have been used to estimate the amount of mercury vapor in the oral cavity. The effect of brushing, chewing and

drinking hot liquids have been included in the measurements to estimate daily dose of mercury.[86,87] A 1985 study[86] estimated the average daily dose of mercury to be 20 μg (micrograms) per day; 29 μg/day for individuals with 12 or more amalgam surfaces; and 8 μg/day for individuals with four or fewer amalgam surfaces.

Analysis of the mercury content of extracted fillings provides another method to determine the amount of mercury released by fillings over extended periods of time. Extracted fillings several decades old were examined using energy-dispersive X-ray spectroscopy (EDX) to determine residual mercury content.[93,94,95]. One EDX study estimated the amount of mercury released from amalgam to be 10 to 20 μg per day per cm^2 surface area.[95] The same study found the amount increased to 250 μg per day when contact was made between an amalgam and gold restoration.

Studying the amount of mercury in bodily excretions provides another method of estimating the level of exposure from amalgam. Comparison of urine mercury levels for amalgam and non-amalgam bearers, some using chelating agents to increase mercury excretion levels, show amalgam bearers typically have mercury levels three to six times higher than amalgam-free controls with notable gender differences.[96,97,98] A 1994 study in Sweden related the number of amalgam surfaces to the emission rate of mercury into the oral cavity and to the excretion rate of mercury by urine and feces.[99] Oral emission up to 125 μg per day were measured and urinary excretions ranged from 0.4 to 19 μg per day. Fecal excretions of mercury ranged from 1 to 190 μg per day. These excretions include both amalgam and dietary sources of mercury. For a middle-age Swedish individual, the systemic uptake of mercury from amalgam was, on average, predicted to be 12 μg per day.

Autopsy studies have been conducted showing mercury levels in adult brains correlate with the number of amalgam fillings.[100] Mercury levels in human fetal and infant tissues correlate with the number of maternal amalgam fillings.[101] Animal studies conducted on sheep and monkeys, using fillings made with radioactive mercury as a tracer, show dental mercury accumulates in the digestive track; kidneys; gums, liver and other tissues (Figure 2).[56,57] The mercury also travels through the placenta from a pregnant animal into the developing fetus[102] as well as into the breast milk.[103]

The fact that mercury vapor escapes from amalgam and enters the body is no longer debated. The issue is how much enters and accumulates in the body and whether it is enough to harm some individuals.

Quantifying Exposure from Amalgam

Question I-1, posed by the FDA, asked the panel to assess the data supporting exposure levels of mercury from amalgam being either 1 to 5 μg/day (7 - 10 fillings), which the FDA currently uses, or 1 to 22 μg/day, argued by the petitioners. The FDA and the petitioners review much of the same literature in estimating levels of exposure. Most published estimates fall in the range of 1 to over 20 μg/day with uptake of up to 100 μg/day reported in extreme cases.[99,104,23] Robert Yokel, one of the three experts asked to address the issue for the FDA as a homework assignment[9], provided a spreadsheet with various literature estimates. If the two camps are reviewing the same literature, what then is the basis for disagreement?

Those supporting the continued use of amalgam use physiological and mechanical arguments to argue in favor of the lower estimates found in the literature. Rod Mackert, professor at the Medical College of Georgia School of Dentistry, was among the public presenters at the FDA meeting. Mackert published a paper in 1997[105] that argued estimates using the Jerome® Analyzer were too high because they did not properly account for differences that occur when an instrument designed to sample large volumes of air is used to measure the small volumes in the oral cavity. Mackert also criticized assumptions related to oral/nasal breathing dynamics and how the effects of chewing were considered.

In its 2009 final rule, the FDA relied on a report by the US Public Health Service published in 1993.[106] The 1993 review agrees with the petitioners that *published* estimates of human uptake of mercury vapor released from dental amalgam range from 1.24 to 27 μg/day.[106] The review, however, also argues that blood mercury levels provide the *best estimate* of daily intake from amalgam restorations. According to the review, comparisons of blood mercury levels for subjects with and without amalgam restorations and studies of subjects before and after amalgam fillings were removed indicate the daily mercury dose to be 1 to 5 μg/day for an adult with 7 to 10 fillings. The validity, however, of using blood mercury levels as a method to assess daily mercury dose from amalgam was challenged by several of the presenters and panelists arguing against amalgam. The Petitioners reference reports from the World Health Organization (WHO)[27] and IAOMT[22] that report literature values ranging from 1 to 20+ μg Hg/day. The IAOMT review includes the work of G. Mark Richardson.

In the early 1990s, Health Canada assigned G. Mark Richardson, a staff specialist in medical risk assessment, the task of evaluating the available literature on mercury and amalgam, and to make recommendations concerning the health impacts of amalgam use in Canada.[107,108,109] In 2010, the IAOMT solicited Richardson to prepare a lengthy two part risk assessment, which was presented to 2010 FDA dental amalgam panel. The first part includes an assessment of exposure levels among amalgam bearers in the US population[11] and the second considers the joint toxicity from mercury vapor, methylmercury and lead.[12] Richardson was one of the primary oral presenters before the FDA Panel on behalf of the petitioners.

Richardson's analysis relies on several studies reporting increase in urine mercury concentration as a function of dental amalgam load (assuming a linear relationship and calculating a slope). Richardson then makes corrections to determine the total mercury excreted via urine and feces and relates the result to dose of mercury per amalgam surface. To assess risk to the US population, Richardson used dental data from National Health and Nutrition Examination Survey (NHANES) compiled by the US National Center for Health Statistics (NCHS). Richardson's assessed risk to the US population includes scenarios for different age groups and assumptions that a certain percentages of restorations were mercury-free.

Richardson's estimates of mercury exposure from dental amalgam range from under 0.2 μg Hg/day to over 58 μg Hg/day depending on factors such as the bearer's age and the number and type of restored tooth surfaces. The high-end estimate corresponds to an adult having every surface of every tooth restored with dental amalgam (128 surfaces) and the lower values corresponds to a toddler with a single filled

surface. Richardson estimates the mean daily mercury exposure for those with exclusively amalgam restorations to be 13 µg/day for adults and 17 µg/day for seniors. Lower values were determined for younger populations and for adults assuming some restorations were mercury-free.[11]

It is important to put the various estimates into context since fillings can vary in volume and exposed surface area. A metric commonly used in dentistry is number of *restored surfaces* which vary less in volume and surface area than fillings. The maximum number of surfaces depends on the tooth; the twelve front teeth have four surfaces each and the remaining teeth have five. A typical adult with 28 teeth has 128 tooth surfaces (excluding wisdom teeth). Richardson indicates that an average filling has 2[11] or 2.5[110] filled surfaces providing a way to convert number of *filled surfaces* to *number of average size fillings*.

Panelists, Joel White, a practicing dentist and professor at the University of California San Francisco who teaches and does research in dental materials, voiced skepticism of the high end estimates based on the fact that restorations are known to last many decades without considerable mechanical failure. White did a quick calculation to show a 600 mg restoration with 50% mercury, releasing 20 µg/day would lose all its mercury in 50 year.[2] White's quick estimate is roughly correct; the actual value is only 41 years strengthening his argument.

> I, as a dental material scientist, have a hard time believing anything over 10 micrograms per day," challenged White, "My clinical experience is that these restorations are not falling out after 50 years or even 25 years. So from a materials perspective, if you're losing that much mercury day after day, the restoration's going to fail mechanically some other way, and frankly I don't see it.[2]

White's calculation, however, does not invalidate Richardson's assessment. Ten two-surface fillings need only release 1.3 µg/day *each* to equal Richardson's reported average exposure level of 13 µg/day for adults. At 1.3 µg/day, it would take over 630 years for a restoration to release all its mercury. Richardson's highest release estimate (based on mean value for adolescents) is 0.8 µg/day per surface. Using the high estimate, a five-surface filling releases 4 µg/day and would take over 200 years to release the 300 mg of mercury found in an average size filling. The five-surface scenario is unlikely since this large restoration would have more than an average amount of mercury to begin with or might be restored with a crown. However, even this artificial worst case scenario does not invalidate Richardson's assessment.

White's criticism is likely targeted at mercury release data presented by Boyd Haley[1,91,92] and other high end estimates.[104] Haley estimates mercury release to be 4.5 to 21 µg/day *per cm^2 amalgam surface area*. These values are reduced when corrected for the smaller surface area of an actual amalgam filling but it seems reasonable to assume that these high release rates would significantly reduce the serviceable life of a restoration. White's clinical observation, however, may not apply to all fillings. Many factors, including contact with other metals, affect the amount of mercury released so large variation is expected. Fillings lasting 25 or 50 years might release less mercury than those that need to be replaced more frequently.

Table 1 compares mercury dose estimates presented at the meeting using mercury per filled surface as a common metric. Unfortunately, the US Public Health Surfaces and WHO reports do not provide the number of surfaces in their estimates so an average value of 20 and a range of 10 to 30 are assumed. For the US FDA data, the range of 1 to 5 µg/day is divided by 20 surfaces to arrive at the range 0.05 to 0.25 µg/day per filled surface. Next, 1 µg/day is divided by 10 surfaces and 5 µg/day is divided by 30 surfaces to arrive at the range 0.1 to 0.17 µg/day per filled surface. The same calculation is done for the Petitioners/WHO estimate. Unfortunately, the number of fillings considered in the WHO estimate is not stated; 22 µg/day may be associated with more than 30 surfaces (a large number of fillings).

Mercury Dose Estimates from Dental Amalgam

Agency or Author	Mercury Exposure (µg per day)	Number of Fillings	Filled Surfaces	Mercury per filled surface (µg per day)
US FDA (US Public Health Service)[106]	**1 to 5**	**7 to 10**	20	0.05 to 0.25
			10 to 30	0.1 to 0.17
Petitioners[5] (WHO, 2003)[27]	**1 to 22**		20	0.05 to 1.1
			10 to 30	0.1 to 0.73
Richardson[11] (Avg Adult)	**12.98**	10.1	**20.2**	0.64
Richardson[11] (Range, Non-Children)	**0.44 to 58.79**	1 to 28	**1 to 128**	0.4 to 0.8 (typically 0.45)

Table 1 Mercury per filled surface is calculated by dividing daily exposure by the number of filled surfaces. The bold font values are documented by the agency or author (Richardson' Table ES-01). Other values are determined assuming either 20 filled surfaces or a range of 10 to 30 filled surfaces. The range 0.4 to 0.8 µg/day per surface is based on Richardson's exposure estimate for adolescents (the maximum and the mean) divided by the number of surfaces. For example, 0.8 was determined by dividing 5.79 µg/day by 7.1 surfaces, mean values for adolescents (Richardson' Table ES-01).[11]

The estimates associated with Richardson in Table 1 are derived from Table ES-01 of his assessment.[11] Richardson considers minimum, maximum and mean exposure estimates for five different age groups (toddlers, children, adolescents, adults and seniors) and four exposure scenarios (differing percentages of amalgam and amalgam-free restorations). To simplify the comparison, Richardson's estimates for toddlers and children are not included in Table 1. Richardson's estimate of the range of exposure for adults and seniors (non-children) fall within the range derived from adolescents. Including toddlers and children would extend the low end of the range to 0.14 µg/day per surface. Considering scenarios where some restorations are mercury-free reduces average mercury exposure but does not affect per surface estimates.

Richardson's typical value of mercury exposure per filled surface is 0.45 µg/day for adults. For example, estimates of the minimum dose for a single surface restoration for adolescents, adults and seniors are 0.49, 0.44 and 0.46 µg/day.[11] Dividing 58.79 µg/day, the maximum dose of mercury for adults, by 128, the maximum number of filled surfaces, gives 0.46 µg/day per surface which is also about 0.45. The mean value for adults, 0.64 µg/day, is larger than the typical value of 0.45 but within the 0.4 to 0.8 µg/day range shown in Table 1.

Richardson published a summary of his risk assessment in 2011 including per surface exposure estimates that differ somewhat from Table 1. The 2011 publication reports, "0.2 to 0.4 µg/day per amalgam-filled tooth surface, or 0.5 to 1 µg/day/amalgam-filled tooth, depending on age and other factors."[110] The higher values in Table 1 are partially explained by the exclusion of toddlers and children.

Table 1 summarizes the mercury dose estimates considered at the FDA panel meeting. Disagreement occurs because of differences in both estimated amount released per filled surface and the number of fillings considered. The FDA daily dose is meant to apply to an *average* number of fillings while Richardson includes a range. Richardson's consideration of a larger range, as well as his stratification by age, was viewed favorably by several members of the FDA science panel. The next consideration is whether estimated levels of mercury exposure from dental amalgam summarized in Table 1 pose a health risk.

Dental Amalgam Risk Assessment

The second set of questions posed by the FDA concerned how the Reference Exposure Level (REL) for elemental mercury – or the level considered protective assuming chronic exposure of the general population and vulnerable subpopulations – should be determined.

The current language adopted by the FDA reads, "The Agency for Toxic Substances and Disease Registry's (ATSDR) and the Environmental Protection Agency (EPA) have established levels of exposure for mercury vapor that are intended to be highly protective against adverse health effects, including for sensitive subpopulations such as pregnant women and their developing fetuses, breastfed infants, and children under age six.[26,112] Exceeding these levels does not necessarily mean that any adverse effects will occur."[13]

Two toxicologists on the panel, Susan Griffin, of the Environmental Protection Agency (EPA) and Michael Dourson, formerly with the EPA, explained how the EPA conducted its risk assessment for mercury.[2] The EPA does not conduct original research but relies on published peer reviewed studies primarily of occupational exposure. Adults exposed to mercury in their work environment are studied to determine the *average* exposure level when certain clinical effects such as hand tremors, ataxia of gait, and/or quantifiable mood or memory disturbances occur. These data are used to determine a lowest-observed-adverse-effect-level (LOAEL) of mercury vapor per volume of air in the environment.

The LOAEL is then divided by an Uncertainty Factor (UF) to determine a Reference Exposure Level (REL) used by policymakers. The UF is designed to account for various unknowns allowing extrapolation of the data to possible vulnerable subpopulations including: children, people unable to work because of poor health and individuals with genetic susceptibilities that might be disinclined to work with mercury.

The UF provides a margin of safety for the LOAEL.

$$REL = LOAEL / UF$$

In 1995, the EPA determined an air quality LOAEL of 9 µg Hg/m^3 and divided the value by a UF of 30 to arrive at a REL of 0.3 µg Hg/m^3.[111] To compare the LOAEL or the REL with the amount of mercury released by dental amalgam into the body one must multiply by the volume of air breathed per day, V, and the proportion of mercury actually absorbed by the body, A. Here, the result will be called the Dose Equivalent LOAEL (DEL). Dividing the DEL by the UF gives the Dose Equivalent REL (DER).

$$DEL = LOAEL \times V \times A$$

William Farland, one of the experts in risk assessment assigned to address the FDA's Homework Assignment,[10] assumed a typical ventilation rate of 20 m^3/day and an 80% absorption rate giving a V x A conversion factor of 16 m^3/day (20x0.8). Multiplying the LOAEL of 9 µg/m^3 by the conversion factor yields an EPA *Dose Equivalent* LOAEL (DEL) of 144 µg/day. Richardson, referencing EPA,[113] uses a ventilation rate of 15.85 m^3/day and the same 80% absorption rate[11] giving a conversion factor of 12.7 m^3/day (15.85x0.8) and an EPA based DEL of 114 µg/day. Richardson's conversion factor results in lower risk thresholds than that of Farland.

Mercury exposure levels above the DEL are expected to cause clinical effects in some adults. Calculated DELs may be compared with the daily dose of mercury from amalgam found in Table 1. The lower estimated DEL of 114 µg/day is twice as much as the highest estimated dose of mercury from amalgam reported by Richardson (~58 µg/day) and over twenty times higher than the maximum value of 5 µg/day used by the FDA in its assessment.

The results above are consistent with the current 2009 FDA guidance, "The amount of mercury measured in the bodies of people with dental amalgam fillings is well below levels associated with adverse health effects. Even in adults and children ages 6 and above who have fifteen or more amalgam surfaces, mercury exposure due to dental amalgam fillings has been found to be far below the lowest levels associated with harm."[13]

To reach the lower estimated DEL of 114 µg Hg/day, 15 amalgam fillings would *each* need to provide a dose of 7.6 µg Hg/day, well above the highest dose estimates found in Table 1.

Richardson criticized the EPA LOAEL as being too high because it included a significant percentage of chloralkali workers who are concurrently exposed to a chlorine gas environment that offers partial protection against exposure to mercury vapor. Griffin called this criticism a "red herring" because the EPA uses other studies in making its assessment as well.

According to Griffin, "Approximately 250 people total from the 3 studies, of which only 12 were chloralkali workers, the rest were dentists, fluorescent lamp workers."[2]

Because of the format, Richardson was unable to respond to Griffin's characterization during the panel meeting. He has since responded in writing to the FDA with a detailed, referenced argument defending his analysis.[115] Richardson notes that if one considers either specific or collective studies considered relevant by the EPA, then the percentage of chloralkali workers in the cohort is over 40% justifying the refined analysis.

The LOAEL disagreement has a minor effect on the risk assessment. The value determined by Richardson is 6 µg

Hg/m^3 whereas the value determined by the EPA is 9 µg Hg/m^3. Greater disagreement occurs regarding the appropriate UF required to provide an acceptable margin of safety.

Griffin explained that the EPA considers five different areas of uncertainty when determining a UF: variability among human beings, applying animal data to humans, short-term studies applied to lifetime exposure, converting a low-effect level to a no-effect level and what is called a "database uncertainty factor" included primarily to account for data from adults being applied to children.[2] The EPA UF of 30 for mercury vapor includes a factor of 10 for sensitive subpopulations and a factor of 3 due to lack of developmental and reproductive studies.[2,114]

FDA also used the REL determined by the US Agency for Toxic Substances and Disease Registry (ATSDR).[26] ATSDR derives a lower LOAEL than US EPA but uses the same UF of 30. A factor of 10 is included for variability in sensitivity to mercury within the human population and 3 for use of a minimal-effect LOAEL.

Richardson's analysis increases the UF to 100 by adding additional protection for vulnerable subpopulations.[10,11,109] Richardson also references a 2010 study by Lettmeier of 306 mercury burdened adults living in gold mining areas in Zimbabwe and Tanzania avoiding the problem associated with chloralkali workers.[114] Lettmeier determined a LOAEL of 3.5 µg/m^3 and applied the EPA UF of 30 to arrive at an REL of 0.1 µg/m^3. Lettmeier also applied a European UF of 50 to arrive at an REL 0.07 µg/m^3. Lettmeier's smaller REL is similar to Richardson's but derived differently. The California EPA accepts the US EPA LOAEL, but increases the UF to 300 to further protect children, particularly their developing nervous systems, arriving at an even smaller REL.[11,116]

Comparison of Risk Assessment Exposure Levels

Agency or Author	LOAEL µg Hg/m^3	UF	REL µg Hg/m^3	Dose Equivalent LOAEL (DEL) µg Hg/day	Dose Equivalent REL (DER) µg Hg/day
US EPA[111] 1995	9	30	0.3	144	4.8
US ATSDR[26] 1999	6.2	30	0.2	99	3.2
Lettmeier[114] 2010	3.5	50	0.07	56	1.12
Richardson[109] 2009	6	100	0.06	96	0.96
California EPA[116] 2008	9	300	0.03	144	0.48

Table 2 REL is determined by dividing the LOAEL by the UF. Dose Equivalents are calculated by multiplying LOAEL and REL by a ventilation rate of 20 m^3/day and a 0.80 absorption rate.[10] Dose equivalents may be multiplied by 0.7925 for consistency with estimated ventilation rate of 15.85 m^3/day used by Richardson.[11] ATSDR uses the term Minimal Risk Level (MRL) instead of REL; US EPA, US ATSDR, and California EPA use the term Reference air Concentration (RfC).

Table 2 summarizes the various risk assessment factors. The DEL and DER agree with Farland's estimate[10] since they were calculated using the same conversion factors. Similar values are also presented in Koral's IAOMT review.[22] Mercury exposure levels from dental amalgam that are above the DEL are known to be harmful to some adults; those below the DER are considered safe. Exposure levels between the two values are not known to cause harm but exceed the margin of safety provided by the Uncertainty Factor (UF).

The FDA determined the maximum amount of mercury exposure from amalgam to be 5 µg/day. Table 2 shows this is about the same as the DER of 4.8 µg/day determined using the US EPA REL of 0.3. For the average amalgam bearer, this analysis is consistent with the FDA language, "that scientific studies using the most reliable methods have shown that dental amalgam exposes adults to amounts of elemental mercury vapor below or approximately equivalent to the protective levels of exposure identified by ATSDR and EPA."[13]

Note the FDA assessment leaves no safety margin beyond that provided by the Uncertainty Factor. Also, since the FDA assumed an average number of fillings (7 to 10 fillings), anyone with an above average number of fillings falls in the region of potential risk.

Richardson's maximum value of mercury associated with dental amalgam, ~58 µg/day, is below most calculated DELs and about the same as Lettmeier's DEL of 56 µg/day. However, comparing Richardson's amalgam exposure levels (~1 to 58 µg/day) with any of the DERs (0.48 to 4.8 µg/day) indicates that a large portion of the amalgam bearing population is exposed to mercury levels that pose a *potential* health risk. The 0.48 µg/day DER based on the California EPA REL are similar to Richardson's dose estimates for a single amalgam surface. By California EPA standards, more than one filled amalgam surface poses a potential risk.

Figure 4 summarizes the current amalgam debate from the risk assessment perspective. There is less disagreement in the regions determined to be harmful (red regions) compared with the levels considered safe (green regions). Both FDA and Richardson's amalgam release estimates are mostly below levels known to harm some adults (red regions). FDA amalgam mercury dose estimates are considered reasonably safe when compared with US EPA and ATSDR risk assessment values but potentially harmful by the other three standards. Richardson's and WHO's amalgam mercury dose estimates are considered *potentially* harmful according to all the risk assessments shown.

Figure 4 explains why the amalgam debate has continued for over 150 years. The amount of mercury released by dental amalgam falls below levels known to show clinical effects in adults who are occupationally exposed to mercury (red regions). Most healthy adults with amalgam fillings should not experience obvious health problems. However, risk assessments based on occupational exposure cannot determine if anyone in a susceptible subpopulation is clinically harmed by amalgam. The uncertainty factor is a formulated extrapolation. If the margin of safety provided is inadequate, a fraction of the population could experience clinical health problems associated with amalgam. Also, since the LOAEL is based on *observed* adverse effects, the assessment is insufficient to determine if the larger population is suffering *subclinical* effects from dental amalgam.

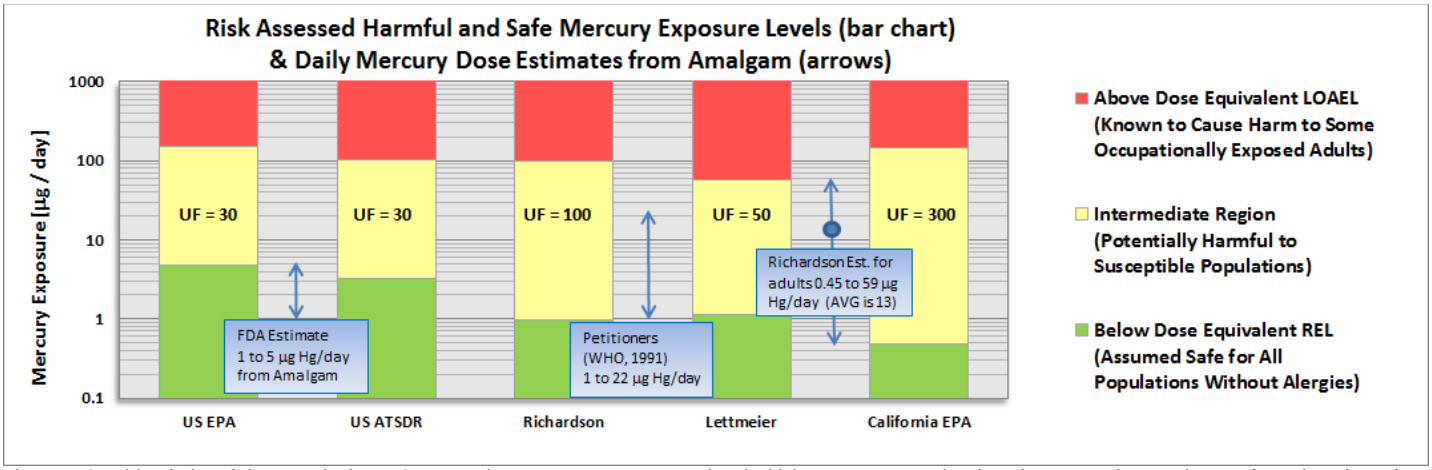

Figure 4 Combined plot of dose equivalent LOAEL and REL mercury exposure levels (risk assessment values) and mercury dose estimates from dental amalgam. Dose equivalents are calculated by multiplying risk assessment LOEAL and REL values by 16. The value 16 is determined by multiplying a ventilation rate of 20m^3/day by 0.8 (80%) absorption rate.[10]

Clinical, Epidemiological & Other Studies

The third set of questions considered by the FDA panel concerned clinical studies of exposure to mercury from dental amalgam. Epidemiological and animal studies were also presented as were biochemical and cellular effects of low-level mercury exposure.

A literature review including clinical and epidemiological studies conducted in 2004 by the Life Science Research Office (LSRO)[16] supports the ADA position that amalgam is safe. The review also identified eight research gaps including: neuropsychological effects of low-level mercury exposure; effects of co-exposure with methylmercury; effects of in utero exposure; effects of exposure from breast milk; reproductive and pregnancy effects from occupational exposure; clinical effects of exposure on dental personal; gender differences in mercury toxicity; and genetic susceptibilities for sensitivity to mercury exposure. A 2010 review by ADA Council on Scientific Affairs[20] concluded that the gaps have only been partially addressed.

Despite the gaps, the authors of the 2010 ADA review conclude, "Overall, studies continue to support the position that dental amalgam is a safe restorative option for both children and adults. When responding to safety concerns it is important to make the distinction between known and hypothetical risks."[20]

The LSRO and the ADA reviews include epidemiological studies of adults and clinical studies of children that largely support the view that amalgam is safe. However, concerns raised by those who oppose the use of dental amalgam are mentioned in the reviews including studies showing subclinical neurological effects associated with dental amalgam and elevated mercury levels in excretions and body tissues.

The ADA review excluded animal studies stating, "Studies were limited to human evaluations, because adverse health effects in laboratory animals do not reliably predict adverse health effects in humans."[20]

The petitioners arguing against the continued use of dental amalgam consider animal studies to be relevant. Amalgam opponents also consider studies showing subclinical and biochemical effects of low-level mercury exposure which the ADA distinguishes as posing only hypothetical risks.

Effects of Low-level Mercury Exposure

Boyd Haley, professor emeritus of chemistry and biochemistry at the University of Kentucky has been studying mercury for decades including the relationship between mercury and Alzheimer's disease.[91] At the meeting, Haley described his mercury release data from fillings placed in water discussed above.[91,92] Haley also discussed differential mercury excretion data showing gender dependence and results from human and animal studies showing subclinical effects associated with low-level mercury exposure.

Haley mentioned studies he conducted showing the deaths of neurons in culture at low mercury exposure levels. He also discussed how mercury induces effects on the immune system, including impairment of neutrophil function and increases inflammation including brain inflammation. Haley described how low levels of mercury disrupt protein formation including the ability for certain proteins to fold properly during formation. Haley also mentioned an association between mercury and cardiomyopathy.

> This is a disease called idiopathic dilated cardiomyopathy. It's what young men die of that die on a football field or basketball field, who are normally healthy, and what was reported in the American College of Cardiology in 1999[117] is that these children have 22,000 times more mercury in their heart tissue than do people who die of other forms of cardiac arrest.[1]

Physician, geneticist and epidemiologist, Mark Geier and his son David Geier, have published several papers regarding autism, mercury and vaccine safety. They described one of their studies finding mothers who had six or more amalgam fillings had a much higher risk of having a child with severe autism versus mild autism.[118] The Geiers cautioned that their study was based on only 100 participants and studies of larger populations are needed.

Anne Summers, metallobiologist from the University of Georgia, has been working in the area of mercury biology for about forty years and coauthored an early review voicing concern about amalgam.[21] She has published work showing that mercury from dental amalgam can increase the

prevalence of mercury- and antibiotic-resistant bacteria in the oral cavity and intestines.[119] She presented data to the FDA panel from monkeys implanted with amalgam showing levels of fecal mercury increased by four orders of magnitude following amalgam placement. She also noted that mercury levels in the gut, some of which was methylated into organic mercury by intestinal bacteria, would exceed mercury levels associated with dietary fish advisories.

Summers also presented data from studies of E. coli bacteria exposed to mercury showing changes in cellular proteins effecting energy metabolism and disturbed metabolic pathways inhibiting the production of adenosine triphosphatase (ATP) within mitochondria. She also showed that mercury increases intercellular free iron and causes other effects that lead to oxidative damage to the cells.

Summer's summarized her findings, "mercury may be involved in many, many diseases and certainly part of what I've shown you is the reason why. There's almost no important system in the cell that is not hit by mercury."[1]

IAOMT dentist David Kennedy, presented an overview of scientific arguments against dental amalgam including various exposure estimates and accumulation in organs including the brain. Kennedy also mentioned the "wide variation in the amount of mercury released from various brands"[1] and faulted the FDA for failing to "set a performance standard based on the amount of mercury released from the various brands."[1]

Kennedy was also one of the first to mention a 2008 paper by Rothwell and Boyd that showed an association with amalgam fillings and hearing loss.[120] Panel member Michael Bates, an epidemiologist from UC Berkeley, thought the paper sufficiently important that it be distributed to the entire FDA panel. The paper was discussed repeatedly among the panelist during the two day meeting.

Epidemiological Studies of Adults

Epidemiological studies of adults largely support the ADA view that amalgam is safe. One epidemiological study, cited in the 2010 ADA review,[20] considered 1663 American veterans and found no significant associations between amalgam exposure and clinical neurological signs of abnormal tremor, coordination, station or gait, strength, sensation, or muscle stretch reflexes or for any level of peripheral neuropathy in the subjects.[121] The study did, however, find a significant association between amalgam exposure and the continuous vibrotactile sensation response. The authors reported this as a subclinical finding not associated with clinically evident signs of neuropathy or any functional impairment. The study did not include more sensitive continuous measures, such as nerve conduction studies, which the study authors noted as a limitation.

A retrospective cohort study that included 20,000 people in the New Zealand Defence Force, led by panelist Michael Bates, investigated the association of amalgam surface area and duration of exposure with several diseases.[71] The three-digit disease codes (International Classification of Diseases, Ninth Revision) were used from hospitalization discharge records to study 15 broad disease categories, 6 specific kidney disorders and 26 specific psychiatric and neurological disorders. The study found no association between amalgam and most of the disease conditions studied including chronic fatigue syndrome and kidney disease.

The New Zealand study, however, did find adjusted hazard ratios of 1.24 for multiple sclerosis (MS) and 1.23 for other paralytic syndromes. A hazard ratio greater than one indicates amalgam is a risk factor for the disease, less than one indicates amalgam protects against the disease and near one indicates amalgam has no effect. The confidence level for these conditions was less than 95% providing limited statistical evidence of an association between amalgam and disease. Statistical confidence tends to increase with the number of cases identified. Of the 20,000 people studied, there were only 7 cases of MS and 14 for other paralytic syndromes suggesting a need for further study. Other studies, including a meta-analysis, have also found a slight, but not statistically significant, increase between the presence of amalgam fillings and MS.[122,123]

The authors include among the key messages, "The possibility that multiple sclerosis could be associated with dental amalgams deserves further investigation."[71]

A limitation noted by the authors was that health outcomes were limited to hospitalization records. The authors note, "Some of the cases of conditions of interest in this study may not have involved hospital admission."[71]

Since many cases of chronic fatigue syndrome may not require hospitalization, restricting the study to hospitalization records is an important limitation. The authors, however, indicated that as long as the undercounting is not differential by amalgam exposure, the limitation would be restricted to a loss of statistical power. The number of cases of chronic fatigue syndrome identified by the study was 132, larger than any of the other psychiatric and neurological disorders studied and larger than all the cases of kidney disorder combined, increasing the statistical confidence. However, it would be valuable to include additional medical information along with hospitalization records in follow-up investigations.

Given the clear statistical power, the authors of the New Zealand study conclude, "There was no evidence that chronic fatigue syndrome is associated with dental amalgams."[71]

The authors of the New Zealand study found hazard ratios below one for all six types of kidney disorders suggesting a possible protective effect of dental amalgam and the kidney. The hazard ratio was particularly low for nephritis not otherwise specified, chronic renal failure and renal failure unspecified, However, the number of cases studied was small and the confidence level below 95% making protective conclusions hypothetical.

The authors of the New Zealand study made no comment regarding any protective effects simply concluding, "In this cohort study there was no evidence of an association between amalgam exposure and adverse kidney effects." [71]

Cohort selection is an important consideration of epidemiological studies. The New Zealand study was heavily weighted to males, 84%, and younger people. Over 85% of the participants were under age 25 at the start of the study and almost 95% were under 45 at the end of the follow-up period. The authors note that the lack of older participants provided insufficient cases to investigate Alzheimer's or Parkinson's disease. Both the New Zealand study and the one of American vets were also restricted to military or former military personnel. The study of 1663 American vets were all Vietnam

era. The study was also confounded by the fact that 677 of the participants were exposed to dioxin during the war and 252 of the participants had confirmed diabetes mellitus. The restricted cohorts of the studies do not reflect a random sample of the larger population.

The authors of the New Zealand study note, "Another strength was consistency of dental treatment across the cohort. All NZDF personnel have received compulsory and equivalent treatment, irrespective of rank. However, among civilians, dental treatment is not equally accessible."[71]

Consistency of treatment, however, also poses a limitation. Factors that vary the amount of mercury released from dental amalgam might have been *over-controlled*. Since mercury release from amalgam is sensitive to alloy composition, manufacturing processes and dental techniques, there is some probability that the cohort was *not* exposed to circumstances resulting in elevated mercury release. Equivalent treatment may also be a limitation of the children's amalgam trials described below.

Because of their statistical design, epidemiological studies are unable to adequately screen for sensitive subpopulations that fall near the edge of a distribution. If only 1 person in 5000 is sensitive to the levels of mercury in amalgam, then a study of 20,000 people is too small.

The studies described above are also limited to dental amalgam as a single input parameter but other factors such as concurrent exposure to other toxins[12] and genetic predisposition[91,124] may be important. Also, since amalgam illness is often described as multi-symptomatic, future investigations should consider the association of amalgam with simultaneous multivariate output parameters instead of single disease conditions.

Despite the limitations, it is reasonable to conclude from the epidemiological studies that dental amalgam alone is not associated with clinical health problems for a large percentage of the younger adult population. This is consistent with the risk assessment described above; the amount of mercury released from amalgam is below the LOAEL values derived from occupational studies of healthy adults. Further studies, including studies of older populations, are required to draw conclusions regarding MS, Alzheimer's disease and Parkinson's disease.

Children's Amalgam Trials

Two clinical studies of the effects of dental amalgam on children weigh heavily on the current FDA amalgam policy: The New England children's amalgam trial[66,67,125,126,127] and the Casa Pia children's amalgam trial.[65,68,69,128,129] *Casa Pia refers to the name of the school in Lisbon Portugal where the study was conducted.* These two studies sparked tremendous discussion from both sides of the debate as well as among the FDA panel members. Mary Tavares, co-principal investigator of the New England trial, explained the work during the public testimony.[1] Michael Martin, project director of the Casa Pia trial, was one of the guest speakers. Both trials were clinical studies of children who had never received dental amalgam and were randomly assigned to receive either amalgam fillings or mercury-free composites. The studies found no statistically significant difference in observed adverse neuropsychological, neurobehavioral, renal effects or intelligence tests between children whose teeth were restored with dental amalgam versus composite resin. The authors of the New England trial did, however, mention in one publication that very small IQ effects cannot be ruled out.[66] A similar study, with similar results, was conducted in China.[130]

Certain subpopulations were *excluded* from participation in both children's amalgam trials. Martin explained the criteria for participation in the Casa Pia trial, "They needed to have an IQ greater than or equal to 67. You can see, blood lead less than 15 micrograms per deciliter, a urinary mercury below 10 mics per liter. And then no existing interfering health conditions and those were primarily, of course, renal and/or neurological problems."[1]

The selection criteria reduce confounding effects simplifying the study. However, as designed, the Casa Pia trial disallows conclusions regarding amalgam safety for children with low IQs, elevated blood lead levels, renal and/or neurological problems or co-exposure to mercury from other sources. Richardson, who considered joint toxicity in his risk assessment,[12] was also critical of the short duration of the children's amalgam trials, arguing that symptoms of chronic mercury exposure may take many years to develop.[11,12]

Panelist Suresh Kotagal, a pediatric neurologist with the Mayo clinic concurred, "You know, there's exposure and there's a long latent period before one becomes clinically symptomatic. So really, there is a synaptic redundancy in the system. We can lose a bunch of synapses but not really have function affected and for example, you know, senile clogs develop in our brain starting around 25, 26 years of age. Mild cognitive impairment doesn't occurs until the fifties or sixties and maybe a decade later, so there is really a period where there is silently things are going wrong, but we are just not aware."[2]

Kotagal, also questioned the use of non-verbal intelligence tests used in the Casi Pia study that may be more appropriate for hearing impaired children, the use of motor nerve conduction velocities instead of testing for changes in sensory neuropathy, and stressed that the children, who were 8 to 10 years old at the start of the study, were too old to assess risk to younger children.

The Casa Pia trial found that urinary mercury concentrations were highly correlated with both the number of amalgam fillings and time since placement and that girls excrete significantly higher concentrations of mercury in urine than boys.[128] The Casa Pia trial also reported a difference in certain urinary porphyrin excretions in children with amalgam compared with children with composites.[129] The porphyrin data resulted in a great deal of discussion.

Porphyrins are a group of ring-shaped, metal-binding organic molecules. The best known porphyrin is heme, the pigment in red blood cells that binds iron. Three porphyrins: pentacarboxyporphyrin, precoproporphyrin and coproporphyrin are known to be associated with mercury body burden. Results from the Casa Pia study show that these three porphyrins were elevated among the amalgam group compared with the composite group but significant difference were found only among younger subjects.[129] The Geiers analyzed the porphyrin data from the Casa Pia study and found increased levels of the same three porphyrins associated with mercury responding in a dose response relationship, to the size and number of amalgam restorations.[131] The Geiers also studied porphyrins

which are not associated with mercury and found no correlation with amalgam.

The FDA relied heavily on the conclusions drawn by the authors of the children's amalgam trials in making its 2009 rule and is expected to carefully consider the concerns the petitioners and panel members raised at the meeting.

Conclusions and Research Gaps

Clinical and epidemiological studies show that the levels of mercury from dental amalgam are not associated with *clinical symptoms* among a large percentage of people with amalgam restorations including children. However, s*ubclinical* and mild clinical effects, including slight hearing loss, are documented. Data are lacking for older adults, younger children and in utero exposure. Further studies are also required regarding MS, Alzheimer's disease and Parkinson's disease.

Another important gap remains as to whether dental amalgam is a contributing factor to *chronic* mercury toxicity, an illness that has *similar* symptoms to acute mercury toxicity but may take years or even decades to develop. The children's amalgam trials have been of insufficient duration to fully address the question. The clinical and epidemiological studies conducted are mainly useful for investigating medical conditions with clearly defined diagnoses. Chronic mercury poisoning and other symptom complexes broadly categorized as *amalgam illness* are currently poorly defined. The condition is alleged to exhibit multiple symptoms with large individual variation. Reviews challenging the existence of amalgam illness suggest psychological conditions may play a role.[19] Reviews opposing dental amalgam support a multivariate model characterizing the variability of the reactions as being similar to pharmaceutical side-effects.[23] Assuming amalgam illness does exist, both sides agree that condition is limited to susceptible subpopulations. The lack of data regarding susceptible subpopulations enhanced the importance of the public testimony at the FDA meeting.

Public Testimony

About fifty individuals were given four minutes each to present their testimony during the public sessions. The panel was allowed time to question the presenters at the end of each session.[1,2]

Andrew Read-Fuller, a fourth-year dental student at the UCLA School of Dentistry, supported the ADA position and argued the lower cost of amalgam was important for the uninsured and people with limited financial resources. Fred Eichmiller, vice president and science officer for Delta Dental of Wisconsin, spoke in favor of dental amalgam and challenged some of Mark Richardson's numbers based on insurance data.

Rod Mackert, professor at the Medical College of Georgia School of Dentistry who has researched the amalgam issue,[14,105] challenged Richardson's risk assessment including Richardson's claim that chloralkali workers are unsuitable as the basis for reference exposure levels, or RELs, because of concomitant exposure to chlorine gas. Mackert argued, "these studies have not depended on mere measurement of air levels of mercury vapor. They include blood, plasma, urine, and tissue levels, and a well-developed understanding of mercury absorption, retention and excretion have been derived from these studies."[1]

Jonathan Knapp, a general family dentist practicing in Bethel, Connecticut and a member of the ADA Council on Dental Practice was one of several dentists who had no doubt that dental amalgam is safe.

> I continue to offer this restorative material as an option for patients in certain clinical circumstances, such as those requiring extensive fillings in molar teeth. Reflecting the national trend, my use of dental amalgam has declined over time, as patients increasingly prefer newer tooth-colored materials. This reduction in use of amalgam owes completely to patients' preference for more aesthetic restorations and not to any question about the safety of amalgam. In fact, I have amalgams in my own teeth and I have used it in treating members of my own family, including one very recently for my wife. If I had any doubt, any doubt about the safety of amalgam, I would never use it to treat a member of my family and I feel as strongly about the health and safety of every one of my patients. If I doubted the safety of amalgam, I simply would not use it.[1]

Steve Koral of the IAOMT argued against the need for the continued use of dental amalgam citing the same trend mentioned by Dr. Knapp, "50 percent of U.S. dentists are practicing without using dental amalgam at all, and 70 percent, roughly, of all fillings are done without using dental amalgam… Mercury exposure is no longer a price we have to pay to be successful in restorative dentistry."[1]

Several mercury-free dentists reported numerous anecdotal cases of health improvement experienced by their patients when amalgam fillings were replaced by mercury free alternatives. Dr. Pentti Nupponen, a dentist with a 30-year career testified.

> We had a Lancaster County dairy farmer who suffered 15 years from small heart attacks. He was sent home to die. As soon as we take -- took the fatal amalgam fillings out, his heart attacks stopped and he went back to work. We had a MS patient, gets out of her wheelchair and walks as soon as she became mercury free. We had a fibromyalgia patient who was for 46 years dealing with terrible pain and drugs. The pain disappeared as soon as she had her mercury fillings taken out. Remember, it's not about us; it's about them.[2]

The most passionate testimony was from dental patients who believe their health was harmed by mercury from dental amalgam. Denise Knight was one of several patients reporting persistent adverse reactions after having her restorations replaced without taking adequate safety precautions. Richard Edlich, professor emeritus of plastic surgery, biomedical engineering, and emergency medicine, University of Virginia, suffers from multiple sclerosis (MS) which confines him to a wheelchair. He indicated the development of his condition might be associated with dental amalgam placed beneath a gold crown and complained about lack of informed consent. Dr. Edlich presented a written petition to the FDA requiring dentists to provide an informed consent brochure to their patients.

Dental hygienist Suzanne Beaudoin testified to developing symptoms of mercury toxicity including "extreme fatigue limiting income, gluten intolerance, gallbladder/liver issues, dizziness, vertigo resulting in falls, hand tremors and tingling sensations, chronic tinnitus and hearing loss."[2] She attributes her mercury symptoms to her 16 amalgam restorations,

mercury laced vaccines and occupational exposure from the dental offices.

Debra Sue Pomeroy Reckmeyer was one of several presenters who spoke about friends and family members who were ill. She told about her nine-year-old daughter who was born with a heart defect that limited her options to dentists with ready access to a hospital. At age four, her daughter had numerous metal crowns and amalgam fillings done over a short period of time after all her teeth dissolved for unknown reasons. Shortly after the dental work, before entering kindergarten, her daughter received numerous vaccines, some containing mercury. The child had been developing normally until kindergarten, when the child experienced developmental delays and neurological problems. At a later age, the child received additional medical intervention for her heart.

> My child now has 59 seizures a day… She can't walk. She can't speak. She acts inappropriately. She is unable to control herself… It was only this summer that we diagnosed all the heavy metal toxicities and that we found about the seizures. We are on a slow alternative method to heal my daughter. She is doing better, but I am gravely concerned."[1]

Benjamin Zander was one of several people, including the author of this overview, who reported recovery of health after replacing amalgam restorations with mercury–free alternatives. Zander is the conductor of the Boston Philharmonic Orchestra and a professor at the New England Conservatory. He provided written and video testimony.[1,132]

> Seven years ago I developed Meniere's disease, which causes violent bouts of vomiting, vertigo and massive hearing loss. Visits to Ear, Nose and Throat specialists throughout the world yielded no results. Because of the violence of these attacks, I had cancel or stop in the middle of several performances that I was conducting.
>
> At the suggestion of a physician at the Paracelsus clinic in San Gallen Switzerland, I had all the mercury and nickel removed from fifteen teeth. This operation was completed by the distinguished American oral surgeon Dr. Robert Evans, of Groton, MA. The results of this process were nothing short of extraordinary. All symptoms of the Meniere's disease suddenly disappeared and have not reappeared.
>
> I shudder to think what diseases this kind of poison is creating in our population.[132]

Professional Engineer Kris Homme attributes her "weird health problems, including vision loss and chronic fatigue" to mercury associated with dental amalgam stating a porphyrin panel confirmed her late-stage chronic mercury poisoning.[1] Treating herself for chronic mercury posing has partially restored her health but her vision loss is permanent. Homme now leads support group for two dozen people who believe they are suffering from chronic mercury poisoning including four PhDs, a dentist and a pediatrician.[1]

Robert Cartland, the author of this overview, was one of several people who presented a reduction of symptoms associated with chronic mercury toxicity following replacement of amalgam fillings with mercury free materials and treatment for mercury poisoning.[1] Records of health symptoms monitored over several years were summarized showing a gradual improvement in health.[133] Cartland also presented summaries of five peer reviewed studies, some including hundreds of patients, showing reduction in symptoms following amalgam replacement.[124,134,135,136,137] Four of the studies are summarized in the 2010 literature review conducted by the ADA council of Scientific Affairs.[20] One study predates the review period.[137] Cartland concluded that his experience of symptom alleviation following amalgam replacement was not unique.

The 2010 ADA literature review mentions several limitations of the amalgam replacement studies. Some studies lacked controls or randomization, and all lacked blinding. Of course, there is no obvious way to design a blind or double-blind amalgam replacement study. However, double-blind studies of low-level *mercury vapor exposure* showing statistically significant hypersensitivity among a subpopulation have been reported.[138] In addition, one amalgam study was a two year follow-up that included patients who replaced their amalgam fillings and a group who did not.[136] Patients who did not replace dental materials did not present any reduction in symptom indices while the group who replaced their fillings showed a significant reduction in intraoral and total symptoms. The reduction in symptoms, however, was not to the level of the general population.

Some of the amalgam removal studies included antioxidant[137] or chelation therapy[124] designed to mitigate the effects of mercury intoxication. Associated treatments appear to improve the level of symptom reduction compared with amalgam removal alone. Unfortunately, associated treatments also confound the effects of amalgam removal –one could argue that the associated treatment rather than the amalgam removal was responsible for symptom reduction. This is also a limitation of many anecdotal reports including Cartland's.[133]

Most of the studies supported the hypothesis that metal exposure from dental amalgam causes ill health in a susceptible population. One removal study conducted without associated treatments arrived at a different conclusion stating, "The finding does not support the hypothesis that removal of dental amalgam will reduce health complaints to normal levels and seriously questions the hypothesis that dental amalgam is an important cause of distress and health complaints."[135]

Most sufferers of amalgam illness, however, hypothesize that in many cases it is the *mercury* that causes the distress and must be removed, along with the amalgam, to reduce health complaints to normal levels. Removal of mercury requires associated treatments like heavy metal chelation.

Despite the limitations, peer reviewed literature, as well as the experience of numerous dental patients and mercury-free dentists show that many people experience some degree of symptom reduction following amalgam replacement. Others have reported little effect and some, like Denise Knight, have experienced an increase in symptoms or the development of other health problems.[1]

While largely anecdotal, the panel gave the public testimony considered attention. Panelist Michael Dourson summarized his thoughts during the panel deliberation.

> When I listen to all of the information from the last couple days, nearly all of it seems relevant to me. So that means

> the 150 years of amalgam implants and then the individual comments we've heard from our other colleagues and the public observers, they all seem relevant to me. And as a risk person I find them to be accepting -- I can accept all of this; not without some critique, but there's a disparity here and I have to ask myself, well, why is there this disparity?[2]

The disparity mentioned by Dourson was a significant portion of the panel deliberation.

Panel Deliberation

The Panel spent the final half-day of the two day meeting discussing and developing consensus statements. The panel was not asked to address whether amalgam should be banned or reclassified –that would be the work of the FDA. The panel was tasked with answering four sets of questions, divided into ten individual questions, to assist the FDA in developing policy. Each panel member was allowed time to express his or her opinion including areas of disagreement. In many cases, the panel arrived at consensus regarding the scientific findings and gaps. Related comments are presented here topically rather than sequentially. The FDA website has complete transcripts of the meeting.[1, 2]

Petitioner and attorney James Love was given 30 seconds during the middle of the deliberations to voice his opinion.

> I've listened all afternoon to what this very prestigious Panel doesn't know and there's a lot of data that we don't know about and a lot of you expressed concerns about an absence of safety data, recent comments notwithstanding. The solution is while we're missing that data, the product goes in Class III.[2]

The panel, however, was instructed by Anthony Watson of the FDA, "…to keep this discussion to the science, avoid any discussion of regulation."[2]

Final analysis and policy decisions would be the responsibility of the FDA.

Benefits of Amalgam

Panel dentist Norman Tinanoff considered the benefits of amalgam to be important, "I did a little reanalysis of the Casa Pia study looking at amalgam survival and composite survival, and from my calculation the amalgam survival was 10% better than the composite."[2]

Neurotoxicology expert Michael Aschner asked, "with all the uncertainties, is it worthwhile using amalgam that contains mercury for a 10-percent benefit? That's my question."[2]

Panel Chair Marjorie Jeffcoat countered, "Yeah, in a comparison study, though, you'd have the risks on the other side."[2]

Panel dentists Van Thompson addressed Tinanoff's comment by citing a recent study of the 12-year survival of composite versus amalgam restorations,[61] "large composites held up very well in the low and medium-risk patients. Only in high-risk was there a difference, but by the end of the 12 years over this study, the difference was very, very small. Failure reasons were different. But in essence, it said the large restorations were holding up quite well."[2]

Consumer Representative Karen Rue voiced general concern regarding the safety issues, "the efficacy obviously has been established, but I feel that the safety issue from everything we've heard in the last 2 days still is in question. And especially when there are quite a few alternatives available."[2]

Panel dentist and IAOMT member Michael Fleming added, "I've been in clinical practice over 30 years and have not used amalgam in 25 and I find this product to be not necessary in the clinical practice of dentistry. I am confounded by the fact that safety is -- or the use of the product is allowed in a population where there aren't -- there isn't enough data to support safety."[2]

Mercury Exposure

The first set of questions (I-1, I-2 and I-3) was related to assessing mercury exposure and bioaccumulation, biomarkers and dependence on factors such as age. Question I-1 asked the panel to assess the data supporting exposure levels of mercury from amalgam being either 1 to 5 micrograms per day, which the FDA currently uses, or 1 to 22 micrograms per day, argued by the Mark Richardson on behalf of the petitioners.

Some panel members communicated support of the methods used by Richardson echoed by two of the people addressing the homework questions. Some of Richardson's assessment scenarios result in dose levels above 58 micrograms of mercury per day (for every tooth surface restored with amalgam).[11] Richardson also stratified his assessment considering different factors including age and scenarios including both amalgam and non-amalgam restorations.

Michael Dourson inquired whether the FDA considered distributions of exposure as well as averages, "The numbers that I'm hearing I believe are the averages?"[2]

Panel Chair Marjorie Jeffcoat confirmed the answer is yes and Dourson continued, "…based on what Dr. Richardson said yesterday is there's another way to look at this, it's whole distribution of intakes, a distribution range, and of course both of these things might be right. The averages might be 1 to 3 and the distribution might be 1 to 22. The question is has FDA tried to replicate the Richardson work or do you espouse the kind of distributions of exposures that might be -- that you might be able to put together with these data?"[2]

Dr. Goering of the FDA responded, "We have not stratified the exposures in the population per Dr. Richardson. And it is something that we'll take a look at."[2]

The concern was echoed by multiple panel members who suggested the FDA should not just rely on *averages* but carefully consider the *distribution* of exposure and consider stratifying the exposure for children and other groups. The panel ultimately pushed the determination of a best estimate of mercury exposure back to the FDA.

Age Related Parameters

Question I-2 asked how age-related parameters factor into the analysis including: inhalation physiology, body weight, number and size of amalgam surfaces (a single filling can have up to 5 surfaces) and other age related differences. Concerns about the vulnerability of the developing brain as well as effects that might be delayed for many years were mentioned by multiple panel members.

Judith Zelikoff suggested methylmercury might be used to assess the risk of prenatal mercury exposure, "I came up with a number of studies in terms of methylmercury and I'm sure Dr. Burbacher can talk about this in greater detail, in which prenatal exposure to methylmercury manifested itself in later time in children, as well as adults in various neurological diseases."[2]

Michael Aschner, a neurotoxicologist and expert in the effects of metals on brain development agreed during a later part of the discussion, "…I think there's plenty of evidence from different studies we've led, for example, with methylmercury, that early exposure can result in late neurodegenerative effects."[2]

Michael Dourson, mercury and methylmercury risk assessment expert, voiced caution on this issue on the first day of the two day meeting, "…I think as we hear about the different mercury compounds, one of the important issues is to consider that comparing methylmercury to ethylmercury to inorganic mercury vapor is like comparing apples to oranges. And I don't think anybody doubts the fact that methylmercury is a toxic compound. But I think we have to put some of these issues into the right perspective..."[1]

Thomas Burbacher has conducted extensive research into the effects of prenatal and early postnatal exposure to methylmercury. He indicated that a maternal fetal model for mercury vapor, similar to models developed for methylmercury, would be of value. He was concerned however, that lack of animal data would make the task difficult.[2]

The consensus was that the data are inadequate to make an assessment regarding a developing fetus and that all the multivariate factors need to be considered by the FDA in developing its risk model for children. The need to consider additional factors such as gender and genetic differences, as well as whether the factors are independent or concomitant, was also expressed by the panel.

Validity of the Urinary Biomarker

Question I-3 (a) addressed the validity of urinary mercury levels in assessing risk of exposure to mercury from dental amalgam. The panel discussed the strengths and limitations of the urinary biomarker especially when applied to children under six and developing fetuses. Thomas Burbacher, expert on the toxic effects of methylmercury, suggested removing the word "risk" to limit the assessment to *exposure.* This suggestion was acceptable to the other panel members and FDA representatives.

Michael Fleming, the IAOMT dentists on the panel, addressed Susan Griffin and Michael Dourson, the panelists who presented the EPA's risk assessment, "I wanted to ask Dr. Griffin or Dr. Dourson, is there a relationship between urine mercury and symptomatology, or what we would call observable effects? My understanding is that we have great variability in that. High urine mercury levels, the patient may not have any symptoms, very low excretion levels. They may have a lot of symptomatology."[2]

Griffin responded,

> I'm not quite sure how to answer that because the human studies that we have are not multiple dose studies; they're basically studies that looked at time-weighted exposures and different occupational settings, be it dentistry, fluorescent lamp factories, whatever. So they were able to equate effects to mercury in hair, mercury in blood, and mercury in urine.
>
> No, there - as I mentioned earlier, you've got the Skaring data that shows you know, strong linear association between urine and mercury and dental amalgams. You have data that shows a strong relationship between urinary mercury and mercury in air. But that's as far as I can go based on the data.[2]

Skaring appears to be a recording error; Griffin was probably referring to the work by Skare and Engqvist.[99]

Dourson added,

> The preferred way to go is biomarker data if you've got it. So you see the lead biokinetic model. Methylmercury, it's levels of methylmercury in blood. Cadmium, it's the amount of cadmium accumulated in the kidney. All biomarkers of exposure are tied to specific effects or lack of effects. And on the basis of, you know, the assessment is done.
>
> In this particular case I haven't seen data that would allow FDA to do that. But if you would cobble those data together that sounds almost not the way to go but if you could put those data together in a way that would be helpful, that would be a preferred way to go. And so I would maybe defer to our FDA colleagues.[2]

Applying urinary biomarker data to children under six and developing fetuses was also discussed.

Suresh Kotagal mentioned, "...I don't see a whole lot of difference between the metabolism of a 5-year old versus an 8-year old and it's -- you know, unless the data's really compelling, that all pre-adolescents or pre-pubescent children be combined so that rather than using 6 and below I would say pre-pubertal and below."[2]

Michael Aschner considered the age of development of the blood/brain barrier to be important adding, "…many of the systems for mercury excretion might not be 100% functionally. The blood/brain barrier is not mature. So maybe a 5 and 6-year old might be the same but a 2-months old and 6-months old are going to be different."[2]

Pediatric dentist Norman Tinanoff suggested further stratification, "…-- maybe in utero; 0 to 3; 3 to 6; and 6 to puberty?"[2]

Amid Ismail agreed with Tinanoff from a dental treatment perspective, "0 to 3 is a unique age and where usually are treated in the OR under anesthesia and receive a lot of restorations. So 0 to 3 is a unique age; and then 3 to 6; and above 6."[2]

Panel Chair Marjorie Jeffcoat summarized, "we do have consensus that urinary mercury levels are the best we have for measuring exposure but we do need to subset out groups of children: fetuses in utero; children from 0 to 3; 3 to 6; and 6 to puberty."[2]

Thomas Burbacher also suggested adding language emphasizing the limitations regarding urinary mercury tests

and that urinary mercury levels are reflective of *current mercury exposure* but not *bioaccumulation*.

Bioaccumulation and Clearance

Bioaccumulation and clearance were the topics of question I-3 (b). FDA representative Peter Goering, a toxicologist at the Center for Devices and Radiological Health, clarified the question, "It's known that mercury will slowly accumulate in several tissues, at least over time, and how do we factor that in when urinary mercury, some people believe, may not reflect that continuing increasing concentration in tissues?"[2]

On the first day of the meeting, before panel deliberation, many of the presenters and panelists discussed the difficulty correlating levels of mercury in urine, blood or feces to symptoms.

Boyd Haley stated that one cannot rely on urinary mercury as a biomarker. He suggested fecal mercury to be a better indication of the amount of mercury traversing the body. Haley also suggested that blood glutathione levels and urinary porphyrin profiles are indicative of body damage due to mercury.[1]

Mark Richardson, in his presentation, also suggested that porphyrin levels be considered when determining a lowest effect level for mercury.[1]

Michael Martin agreed that perhaps the porphyrin profiles might be used as biomarkers for mercury but mentioned that "porphyrin profiles, including these porphyrins, can be affected by antibiotics and other prescription medications, illnesses, and other metals. So much more work would need to be done before considering that."[1]

The limitations regarding *urinary* mercury resulted in some panelist considering fecal mercury as an alternative. During the panel deliberation, Anne Summers was asked by the panel to clarify her work with monkeys relating *fecal* mercury to bioaccumulation. There was some data on animals, explained Summers, but limited data available for humans.

Suresh Kotagal argued that more advanced tools should be used to assess the effects and risk of mercury including, "quantitative EEG, MR spectroscopy, and functional MRI. …to determining whether there is any dysfunction prior to clinical manifestations appearing."[2]

Panelist Michael Aschner, a researcher in the area of neurotoxicology, disagreed based on practical considerations, "these are very expensive studies and you might be able to do it in a very small population."[2]

Panelist Amid Ismail, added, "we're not doing studies here because there's a policy decision that needs to be made and needs to be made within a short period of time."[2]

The panel converged on acceptance that an assessment of bioaccumulation and clearance was not available. Dr. Jeffcoat summarized the panel's assessment, "So do we have consensus that we really do not have the information to answer that question?"[2]

Michael Fleming, the IAOMT dentists, elaborated, "I think we can acknowledge that there is bioaccumulation and clearance differences... But what we lack are data to establish the nature of the bioaccumulation phenomenon and the clearance issues that vary between subgroups and all the rest."[2]

Reference Exposure Level

The second group of questions, (II-1, II-2 and II-3) was related to the determination of the appropriate LOAEL (II-1) and uncertainty factor (II-2) used to determine a reference exposure level (II-3) for safety policy. The panel was asked to weigh the merits of the approaches taken by the EPA and Mark Richardson. Technically, the resulting safe exposure level is defined as an RfC (reference concentration) which is defined for safe *continuous* exposure. However, the model used would be similar to the one used to determine an REL described above.

Gary Ginsberg in answering the homework assignment suggested considering more modern risk assessment models such as "the option of low dose linear modeling for agents such as mercury that have high potential for background interaction and no evidence for a threshold."[8] This idea was discussed favorably by multiple panel members.

The panel did *not* recommend a revised Reference Exposure Level (REL) but did suggest that FDA reconsider its risk analysis in light of recent studies and carefully consider sensitive subpopulations. Michael Fleming, the IAOMT dentist on the panel, emphasized that the panel was *not* endorsing the use of the EPA REL and panel Chair Marjorie Jeffcoat concurred.

Dentist and material scientist Joel White summarized the situation, "It seems to me, and I want to echo, that LOAELs are very close amongst the four studies. So if FDA were to do one thing it would be batten down the uncertainty factors with the new data."[2]

"FDA has some of the best risk assessment experts in the world," acknowledged Michael Dourson formerly of the EPA, "So what I would like to enjoin, and you've already heard -- everyone is doing this, is to ask our FDA scientists, who are really very good at this, to look at these new data, the data since 1995, and really kind of develop your own reference concentration."[2]

Several of the panel members assumed that this reassessment would lead to substantial change in health policy regarding amalgam that would need to be communicated to doctors, dentists and the public.

Epidemiologist Michael Bates asked the FDA representatives about the policy implications of reassessing the REL, "…we've learned yesterday that it doesn't matter, you know, where we set the REL, RfC, some people -- some substantial proportion of people are likely to exceed it in terms of the dental amalgams. So what difference does it actually make whether we raise it or lower it or change it in any way? What regulatory action potentially could flow from that?"[2]

FDA representative Anthony Watson reiterated that the FDA would need to establish policy but "It's important to see what the experts out there think outside of FDA when we're making these decisions."[2]

Clinical Studies and Health Effects

The third set of questions considered by the panel was related to the clinical studies, health effects and modification of FDA

guidance language. The first of the set (III-1) was to "assess the strengths and the weaknesses of the clinical studies on dental amalgam, including whether appropriate endpoints were evaluated."[2] The second of the set (III-2) asked, "Do the clinical studies support a relationship between exposure to mercury vapor released from dental amalgam and adverse health effects associated with renal, immunological, allergic, neurobehavioral or psychological function? Are there other adverse health events identified by these clinical studies?"[2]

Michael Bates, principle investigator of the New Zealand study[71], argued that the committee should communicate important research gaps to the FDA requiring further studies. "I would in that regard particularly like to mention the neurodegenerative diseases, MS, Alzheimer's and Parkinson's… I can say that the data on these three outcomes are very inadequate and really one couldn't make any judgment whatsoever."[2]

Bates also stressed the importance of the study on hearing loss[120], "But here we have a paper which actually shows an apparent effect based on number of amalgam fillings."[2]

Panel dentist Joel White was clear, "I do not see any scientifically credible reason to recall or curtail or change the use of amalgam. …But on the other hand, we have environmental issues, that's clear, and lowering mercury in the environment is a good thing."[2] He maintained, "…there is no causal link between these different disease states and the use of amalgam that's shown by the science. However, I'm swayed by all these compilations of case studies."[2]

Panel Chair Marjorie Jeffcoat summarized the consensus statement, "Are there other adverse health events identified by these clinical studies? These clinical studies really didn't answer this question very much. I mean, these clinical studies say that in the population as a whole, it looks good. But they did not really get at who might be or identifying who might be the susceptible subpopulation."[2]

Susceptible Subpopulations and Children

The need to better protect susceptible subpopulations was the primary development in the amalgam debate. Those purporting amalgam safety acknowledge the existence of a small number of people with easily identifiable and immediate *allergic* reactions to mercury or the other metals in amalgam.

The 2009 FDA language reads,

> Some individuals have an allergy or sensitivity to mercury or the other components of dental amalgam (such as silver, copper, or tin). Dental amalgam might cause these individuals to develop oral lesions or other contact reactions. If you are allergic to any of the metals in dental amalgam, you should not get amalgam fillings. You can discuss other treatment options with your dentist.[13]

Multiple panel members, including those supporting the continued use of amalgam, however, suggested that reactions to amalgam may develop slowly, may be difficult to identify and may not be extremely rare.

Toxicologist Judith Zelikoff spoke at great lengths about metal sensitivity. "I don't know how you define extremely rare, but in searching the literature, I found anything from 2% to 5% of the North American population. …But I don't think having a 2 or 5% allergy is low for the North American population."[2] It was later clarified that she was referring to mercury specifically versus amalgam.

Susan Griffin of the EPA stressed the importance of protecting susceptible subpopulations, "I think that the studies listed here provide very compelling evidence that there is no effect level that can be identified in a general population and I do think that this gives us a handle on effect levels in the general population, but I want to also echo my concerns that there does appear to be a very susceptible subpopulation to immunological effects."[2]

Members from both sides of the debate also concurred that more adequate measures needed to be taken to protect children and developing fetuses.

Panel dentist Amid Ismail favored the continued use of amalgam but was also concerned about the lack of data for children under 6 years of age and other vulnerable subpopulations. "..we have to find ways to recognize that there are some patients who cannot -- should not have amalgam. I am not in favor of banning amalgam because I want to keep the option for the patient."[2]

Pediatric neurologist Suresh Kotagal made clear his opinion regarding children, "infants and children need to be addressed separately than the adults because of their increased risk. And I think that there really is perhaps no place for mercury in children."[2]

Panel dentist Van Thompson agreed, "Definitely not in pregnant women and definitely not in those below 6 years of age."[2]

Adequacy of Current FDA Guidance Language

Question III-3 was directed at specific language the FDA adopted following its 2009 decision:

> Clinical studies have not established a causal link between dental amalgam and adverse health effects in adults and children 6 and older. In addition, two clinical trials in children age 6 and older did not find neurological or renal injury associated with amalgam use.
>
> The developing neurological systems in fetuses and young children may be more sensitive to the neurotoxic effects of mercury vapor. Very limited to no clinical information is available regarding long-term health outcomes in pregnant women and their developing fetuses, and children under 6, including infants who are breastfed.[13]

The panel was asked to discuss whether FDA appropriately represented the strengths and weaknesses of the available clinical data. The discussion focused on the above statements, rather than the entire FDA disclosure language, because these statements were the basis for the remaining language adopted by the FDA.

Norman Tinanoff suggested adding a sentence, "There may be certain populations that are more sensitive to the mercury in dental amalgam."[2]

Thomas Burbacher implied eliminating the term 'under 6', "I'd like to extend that to children, because we were just talking about that long-term health outcomes have not been studied in

children, so it's not just limited to fetuses and children under 6."[2]

Suresh Kotagal suggested, "inserting 'age 6 and older with follow-up of up to 7 years', because there was no long follow-up. And also … 'It is not known whether the lack of toxicity in children will endure with the longer follow-up'."[2]

Panel dentist Joel White was clear about what needed to be communicated:

> Because of the unknown risks, dentists should consider not placing in pregnant and nursing women. Dentists should consider not placing in patients with neurologic or kidney impairment or function. Avoid placing in patients who have allergic or hypersensitivity to mercury. The labeling should also include some language regarding should consider reducing mercury exposure levels to the environment, to the patient and to personnel, as well as using accepted protocols for safe handling, safe use, safe disposal and safe removal from patients.[2]

Some of the panelist wished to express opinions regarding other statements made in the 2009 FDA document. Michael Bates noted, "…it states in the second paragraph below the box, that reliable methods have shown that dental amalgam exposes adults to amounts of elemental mercury vapor below or approximately equivalent to the protective levels of exposure. I'm not sure, based on Dr. Richardson's data yesterday, that that is true. It seems like quite a few people could be exposed to levels above those."[2]

Dr. Jeffcoat concurred, "I believe, if the FDA chooses to act on our suggestion, those numbers may -- Dr. Richardson's numbers may be recalculated."[2]

Judith Zelikoff, an environmental toxins expert, challenged another statement in the FDA language, "FDA estimates that the estimated daily dose of mercury in children under age 6 with dental amalgams is lower than the estimated daily adult dose. I find that difficult to believe and I also think that that should not be included."[2]

Michael Fleming concluded, "I think something needs to change. I think the ideas on this label are fantastic and I think that those changes should be considered and considered quickly."[2]

Weighing Risk Assessment & Clinical Studies

The final question (IV) asked, "Based on your answers to these three sets of questions, discuss how FDA should weigh risk assessment and clinical studies in considering its regulatory approach to dental amalgam."[2]

This question generated questions from the panel but the consensus was that the risk assessment follows from the clinical studies. Bates summarized, "I don't see them as being either/or in terms of weighing one against the other. I think they're quite complementary."[2]

Dourson concurred, "So again, you don't have to separate it, you know, from a risk perspective or a clinical perspective, because if the risk people are doing their job, they're listening to their clinicians and their colleagues in that area."[2]

Communicating Policy Decisions

Jo-Ellen De Luca, the Patient Representative on the panel emphasized the need to communicate any resulting policy revisions in a manner understandable to the public. "I would like to ask the FDA, and indeed information from the Panel, to come up with a more simplified risk assessment in layman's terms so that patients could actually take a look at it and say, "Ah, this is what they're talking about."[2]

Joel White agreed and also stressed the need for clear communication with dental and medical professionals,

> And the other part that's very important to tie into is put it in a digestible format, both for the patients but also for the profession. I want to know that that subpopulation, that subgroup, what the characteristics are that they may have an adverse event. I want it -- as a clinician I want to know where that threshold is or where I start to push that boundary so that I can be more attune to looking for the adverse events. That will make me a better dentist, the profession better, and patients be more trusting of, you know, dentistry and the FDA.[2]

Consumer representative Karen Rue pushed the communication model further, "I would like to suggest that it's done in collaboration with all the dental societies because as wonderful as the FDA website it, that's not where people go to get their information; it's within the dental offices and where they receive the service."[2]

William O'Brien suggested a pharmaceutical model be considered in the form of an adverse event chart. "They list all the possible symptoms and hopefully you don't get those symptoms. But they do expose that publicly, as to all the possible symptoms that have been reported with the drug."[2]

The panel's Industry Representative Michael Bui suggested establishing a Risk Evaluation and Mitigation Strategy (REMS).

> I'm very concerned about mercury and I think that's something that the FDA might consider, imposing something like REMS that would require patient registries. That would provide significant data to study long-term outcomes.
>
> Another thing that the FDA might consider usually on a REMS component is that they would require patient education or at least, you know, for healthcare professional education to educate health professionals about a product itself.[2]

The meeting concluded with Anthony Watson of the FDA thanking the panel and other participants, "I just wanted to thank the Panel and especially Dr. Jeffcoat. The FDA really appreciates everyone's input. And I also want to thank the public speakers and the invited speakers who came. I think your testimonies are very important. We're going to go back, as I mentioned, and really hit this and hopefully we'll come out with something that everybody can be proud of."[2]

Global Debate

The safety of dental amalgam is also being debated globally. Global limitations on the use of mercury products including dental amalgam are being discussed in world mercury treaty negotiations held by the United Nations Environment

Programme (UNEP). The work of the UNEP intergovernmental negotiating committee will be carried out over five sessions with the goal of developing a global, legally binding instrument on mercury. The first session was held in June, 2010 in Stockholm, Sweden and the second in January, 2011 in Chiba, Japan. The other three sessions are scheduled to meet in the fall of 2011, in mid 2012 and in early 2013.

Most countries including the United Kingdom, France and Italy allow the unrestricted use of dental amalgam. The European Commission currently considers dental amalgam a safe and effective material.[18] One month after the FDA meeting in the US, a review was written critically opposing several conclusions made by the European Commission[25] and panels are being convened to reconsider current policy.

Health Canada takes a more precautionary approach to dental amalgam based on the work of Mark Richardson. Dentists are encouraged to consider non-mercury filling materials for children and, whenever possible, fillings should not be placed or removed from the teeth of pregnant women. Health Canada also states that amalgam fillings should not be used in patients with impaired kidney function, or allergic hypersensitivity to mercury and should not be placed in contact with other metals.[139] Germany, Austria and Japan have similar restrictions on the use of dental amalgam.

Denmark, Norway and Sweden have effectively banned the use of dental amalgam. Norway's ban went into effect January 1, 2008 as part of a comprehensive ban of mercury products implemented by the Ministry of the Environment.[140] Exceptions for patients who must be treated under general anaesthesia or who are allergic to ingredients in other dental fillings were allowed until December 31, 2010.[141] A similar ban of mercury products went into effect in Sweden on June 1, 2009 after environmental and health concerns were considered.[142] Norway and Sweden also support a comprehensive ban of mercury products in the European Union and globally.

Maths Berlin, Professor Emeritus of Environmental Medicine with extensive experience investigating the effects of mercury on animals and humans, chaired a 1991 World Health Organization Task Group on Environmental Health Criteria for Inorganic Mercury. He prepared a report in 2003 as part of a special investigation for the Swedish Government on amalgam related health issues. Maths Berlin's assessment considered over 700 articles published during the period from November 1997 to November 2002[23] as a follow up to a similar assessment made in 1997. The Swedish government has an English translation of Berlin's assessment available on its website referring to it as an "internationally acclaimed annex."[23]

Maths Berlin assessment concluded,

> For medical reasons, amalgam should be eliminated in dental care as soon as possible. This will confer gains in three respects. The prevalence of side-effects from patients' mercury exposure will decline; occupational exposure to mercury can cease in dental care; and one of our largest sources of mercury in the environment can be eliminated.[23]

The document including Berlin's annex was updated in 2004 to include a summary preface communicating the work of a Swedish government commission charged with "investigation and care of, people who associate their symptoms with dental materials."[23]

The preface includes the concerns of the Swedish government commission,

> Great efforts have thus been made to improve the care and consideration these patients receive. Nonetheless, those who relate their symptoms to amalgam or other dental materials still feel that they are meeting a nonchalant response in the care services, and not receiving the treatment they believe that they need. These patients, who often have a long history of illness, have undergone many courses of treatment with only a limited effect on their symptoms. Many have, in due course, had their fillings removed.
>
> In some cases, they have reported mitigation of their symptoms as a result. This is the background to the Government's appointment of a Special Investigator to propose measures aimed at boosting knowledge of health problems relating to amalgam and other dental materials, and to improve care and consideration for patients who associate their symptoms with such materials.[23]

This Swedish commission's concerns were echoed by several members of the FDA panel including the panel's Industry Representative Michael Bui when he suggested establishing a Risk Evaluation and Mitigation Strategy (REMS) in the US.

The debate on whether to ban, phase-out, or continue the use of dental amalgam continues in the US and abroad. However, there is emerging consensus regarding the need to improve consumer education regarding dental amalgam and to better protect susceptible subpopulations. There is also growing consensus to improve the care and consideration of patients who associate health symptoms with dental amalgam and the need to better educate the dentists and doctors who care for these patients.

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Disclaimer: The opinions expressed are those of the author and do not necessarily represent the opinion of the author's employer or any other organization and are not to be considered health advice.

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References

FDA Meeting Transcripts and Materials

References 1 to 12 are materials from the 2010 FDA meeting available on-line using the link below.

www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/DentalProductsPanel/ucm235085.htm

Materials from the 2006 meeting of the Dental Products Panel are also available on-line (under the heading, Dental Products Panel, September 6 and 7, 2006 with Peripheral & Central Nervous System Drugs Advisory Committee):

http://www.fda.gov/ohrms/dockets/ac/cdrh06.html

Reference 13, is a summary of the 2009 FDA rule including guidance language. The complete text is included at the end of this document. Quoted text from reference 13 is shown in blue in the body of this document.

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Dental Products Panel Roster
December 14-15, 2010

Name	Affiliation	Role	Expertise
Marjorie K. Jeffcoat, D.M.D.	University of Pennsylvania Philadelphia, PA	Panel Chair	Periodontistry, Clinical Studies
Kenneth J. Anusavice, PhD, DMD	University of Florida Gainesville, FL	Regular Member	Operative Dentistry, Biomaterial Science, Prosthodontic Materials, Control-release Agents
John J. Dmytryk, D.M.D., Ph.D.	The University of Oklahoma Oklahoma City, OK	Regular Member	Periodontistry, PhD in Biology
Amid I. Ismail, B.D.S., Dr.P.H., M.B.A.	Temple University Philadelphia, PA	Regular Member	Epidemiology, Public Health, Evidence Based Dentistry, Disparity Research
Clark M. Stanford, D.D.S., Ph.D.	University of Iowa Iowa City, IA	Regular Member	Prosthodontistry, Developmental Biology and Stem Cell Differentiation on Metal Surface
Joel M. White, D.D.S., M.S.	University of California San Francisco, CA	Regular Member	Clinical Dentistry, Dental Materials
Michael Aschner, Ph.D.	Vanderbilt University Medical Center Nashville, TN	Temporary Member	Neurotoxicology, Toxicity of Metals and Effect on Brain Development
Michael Bates, Ph. D.	University of California Berkeley, CA	Temporary Member	Epidemiology, Principal Investigator of New Zealand Dental Amalgam Study
Thomas M. Burbacher, Ph. D.	University of Washington Seattle, WA	Temporary Member	Methylmercury Developmental Toxicology
Michael Dourson, Ph.D.	Toxicology Excellence for Risk Assessment Cincinnati, OH	Temporary Member	Toxicology, Environmental Risk Assessment, Development of Toxicity Values including Mercury
Michael Fleming, D.D.S.	Private Practice Durham, NC	Temporary Member	Dental Clinical Sciences, Oral and Systemic Health
Susan Griffin, Ph.D.	U.S. Environmental Protection Agency Denver, CO	Temporary Member	Toxicology, Exposure Risk Assessment, Development of Toxicity Values
Janine E. Janosky, Ph.D.	Austen BioInnovation Institute Akron, OH	Temporary Member	Biostatististics, Community Health
Suresh Kotagal, M.B, B.S.	Mayo Clinic Rochester, MN	Temporary Member	Pediatrics, Pediatric Neurology
William O'Brien, M.S., Ph.D.	University of Michigan Ann Arbor, MI	Temporary Member	Metallurgical Engineering, Dental Materials, Release of Mercury from Dental Amalgam
Van P. Thompson, D.D.S., Ph.D.	Dept. Biomaterials & Biomimetics New York, NY	Temporary Member	Dentistry, Dental Biomaterials and Biomimetics
Norman Tinanoff, D.D.S.	University of Maryland Baltimore, MD	Temporary Member	Pediatric Dentistry, Clinical Trials, Preventive Agents
Judith Zelikoff, Ph.D.	Institute of Environmental Medicine Tuxedo, NY	Temporary Member	Environmental Medicine, Immunotoxicology, Inhalation Toxicology, Emphasis on Metals
Michael D. Bui, D.D.S., M.P.H., J.D	Bayer Healthcare Pharmaceuticals Montville, NJ	Industry Representative	Clinical & Regulatory Policy
Jo-Ellen De Luca*		Patient Representative	
Karen R. Rue**	Acadiana Office of Griswold Special Care Lafayette, LA	Consumer Representative	
Olga I. Claudio, Ph. D.	Food and Drug Administration Silver Springs, MD	Designated Federal Officer	

* Ms. JoEllen De Luca serves as a Patient Representative to the CDER Crohn's Disease, Colon Cancer and Immune diseases drug panels.
** Ms. Karen R. Rue serves as a Consumer Representative to the CDRH General Hospital and Personal Use Devices Panel.

The FDA roster lists the regular members as "voting" and the temporary members and "non-voting"; no vote, however, was taken at the 2010 meeting.

Summary of 2009 FDA Dental Amalgam Rule

Source: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DentalProducts/DentalAmalgam/ucm171120.htm

This document is provided to facilitate understanding of the December 14 and 15, 2010 meeting of the Dental Products Panel of the Medical Devices Advisory Committee of the FDA discussed in this paper.

The reader is urged to consult the FDA website for up-to-date policy regarding dental amalgam.

Appendix I: Summary of Changes to the Classification of Dental Amalgam and Mercury

On July 28, 2009, FDA issued a final rule that: (1) reclassified mercury from a class I (least risk) device to class II (more risk) device; (2) classified dental amalgam as a class II device; and (3) designated a special controls guidance document for dental amalgam.

The special controls guidance document identifies the risks to health of dental amalgam and recommends mitigation measures to address those risks. The potential risks to health of dental amalgam identified in the guidance document are: (1) exposure to mercury; (2) toxicity and adverse tissue reaction; (3) corrosion and mechanical failure; (4) contamination; and (5) improper use. The guidance document recommends measures to mitigate these risks, including certain labeling recommendations

The guidance document recommends the following specific labeling:

- Warning regarding the presence of mercury in the device and the possibility of harm if vapors are inhaled
- Disclosure of mercury content
- Contraindication for use in persons with a known mercury allergy or sensitivity
- Disclosure of certain information about the physical properties of the device
- Certain precautions with respect to use; e.g., the device is intended for single use only, it should be used with adequate ventilation, and it should not directly contact other types of metals
- Information for use including the following, or an equivalent, statement:

"Dental amalgam has been demonstrated to be an effective restorative material that has benefits in terms of strength, marginal integrity, suitability for large occlusal surfaces, and durability.[1] Dental amalgam also releases low levels of mercury vapor, a chemical that at high exposure levels is well-documented to cause neurological and renal adverse health effects.[2] Mercury vapor concentrations are highest immediately after placement and removal of dental amalgam but decline thereafter.

Clinical studies have not established a causal link between dental amalgam and adverse health effects in adults and children age six and older. In addition, two clinical trials in children aged six and older did not find neurological or renal injury associated with amalgam use.[3]

The developing neurological systems in fetuses and young children may be more sensitive to the neurotoxic effects of mercury vapor. Very limited to no clinical information is available regarding long-term health outcomes in pregnant women and their developing fetuses, and children under the age of six, including infants who are breastfed.

The Agency for Toxic Substances and Disease Registry's (ATSDR) and the Environmental Protection Agency (EPA) have established levels of exposure for mercury vapor that are intended to be highly protective against adverse health effects, including for sensitive subpopulations such as pregnant women and their developing fetuses,

breastfed infants, and children under age six.[4] Exceeding these levels does not necessarily mean that any adverse effects will occur.

FDA has found that scientific studies using the most reliable methods have shown that dental amalgam exposes adults to amounts of elemental mercury vapor below or approximately equivalent to the protective levels of exposure identified by ATSDR and EPA. Based on these findings and the clinical data, FDA has concluded that exposures to mercury vapor from dental amalgam do not put individuals age six and older at risk for mercury-associated adverse health effects.

Taking into account factors such as the number and size of teeth and respiratory volumes and rates, FDA estimates that the estimated daily dose of mercury in children under age six with dental amalgams is lower than the estimated daily adult dose. The exposures to children would therefore be lower than the protective levels of exposure identified by ATSDR and EPA.

In addition, the estimated concentration of mercury in breast milk attributable to dental amalgam is an order of magnitude below the EPA protective reference dose for oral exposure to inorganic mercury. FDA has concluded that the existing data support a finding that infants are not at risk for adverse health effects from the breast milk of women exposed to mercury vapors from dental amalgam."

The guidance document also recommends that the device and its individual components, mercury and amalgam alloy, meet the performance specifications contained in ISO 24234; 2004(E), Dentistry – Mercury and Alloys for Dental Amalgam, the recognized consensus standard identified in the guidance document.

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[1] Dental Amalgam: A Scientific Review and Recommended Public Health Service Strategy for Research, Education and Regulation; Public Health Service, U.S. Department of Health and Human Services, January 1993.

[2] Liu, J. et al., "Toxic effects of metals," Casarett & Doull's Toxicology: The Basic Science of Poisons, Chapter 23, pp. 931-979, McGraw-Hill Medical, New York, New York, 2008.

[3] De Rouen, T. et al., "Neurobehavioral Effects of Dental Amalgam in Children, A Randomized Clinical Trial," Journal of the American Medical Association, Vol. 295, 1784-1792,No. 15, April, 19, 2006.
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[4] Agency for Toxic Substances and Disease Registry (ATSDR) and Research Triangle Institute, Toxicological profile for mercury, U.S. Dept. of Health and Human Services, Public Health Service, Atlanta, Georgia, 1999.
United States Environmental Protection Agency (EPA), "Integrated Risk Information System (IRIS) Screening-Level literature Review" – Mercury, elemental, 2002.