SUMMARY MINUTES

JOINT MEETING OF THE DENTAL PRODUCTS PANEL AND PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE

September 6, 2006

Gaithersburg Holiday Inn
Gaithersburg, MD.

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Dental Products Panel Attendees

Chairman:

Richard Burton, DDS
University of Iowa

Consumer Representative:

Michael Fleming, DDS
Dentist, Private Practice

Industry Representative

Mason Diamond, DDS
TyRx Pharma, Inc.

Patient Representative:

Theresa A. Cowley
The TMJ Association

Members:

Solomon Amar, DDS, PhD
Boston University

Yiming Li, DDS, PhD
Loma Linda University

Man Wan Ng, DDS MPH
Children's Hospital

William O'Brien, MS, PhD
University of Michigan

Domenick T. Zero, DDS, MD
Indiana University

John R. Zuniga, PhD, DMD
University of Texas

Executive Secretary:

Michael E. Adjodha

Peripheral & Central Nervous System Drugs Advisory Committee Attendees

Chairman:

Karl D. Kieburtz, MD, MPH
University of Rochester

Consumer Representative:

Lilly K.F. Jung, MD, MMM
Swedish neuroscience Institute

Industry Representative:

Roger J. Porter, MD
Consultant

Temporary Voting Members:

Michael Dourson, PhD
Toxicology Excellence for Risk Assessment

Lynn R. Goldman, MD, MS, MPH
Johns Hopkins University

Margaret Honein, PhD, MPH
Centers for Disease Control and Prevention

Curtis D. Klaassen, PhD
Kansas University

Michael I. Luster, PhD
National Institute for Occupational Safety and Health

George Wesley Taylor, III, DMD, DPH
University of Michigan

Members:

Michael Aschner, PhD
Vanderbilt University

Larry B. Goldstein, MD
Duke University

Michael D. Hughes, PhD, MSc
Harvard University

Sandra F. Olson, MD
Northwestern University

Matthew Rizzo, MD
University of Iowa

Ralph L. Sacco, MD, MS
Columbia University

Executive Secretary:

LT Darrell Lyons, BSN, RN

CALL TO ORDER

Dr. Burton called the meeting to order at 8:15 a.m. Executive Secretary Adjodha explained that the joint committee will be chaired by Dr. Burton in the mornings and Dr. Kieburtz in the afternoons. He read the conflict of interest statement into the record. All members and consultants were in compliance, and waivers were issued to Dr. Goldstein and Dr. Olson. Dr. J. Rodway Mackert, a guest speaker, acknowledged a financial interest in and professional relationship with a firm at issue. Michael Dourson, Lynn Goldman, Peggy Honein, Curtis Klaassen, Michael Luster, and George Wesley Taylor were appointed temporary voting members. Michael Aschner was made a full voting member. Dr.Burton had the Panel members introduce themselves and noted the presence of a quorum.

Dr. Alderson explained the nature of the joint advisory committee and how it would be run. The meeting was to review the draft FDA White Paper that summarizes and interprets the literature since 1997 on the safety of mercury released from dental amalgams and assess whether the research merits a change to the conclusions about risk assessments. The meeting was also an opportunity to receive public comment.

BACKGROUND

Dr. J. Rodway Mackert of the Medical College of Georgia gave a presentation on dental amalgam and other restorative materials. Dental amalgam is supplied in capsules that contain the components, liquid mercury and powdered amalgam alloy, usually a mixture

of silver, copper, and tin. The components are mixed in an amalgamater and become a pliable mass. Intermetallic compounds form in gamma and gamma 2 phases, and there is no free elemental mercury remaining in a set dental amalgam. Amalgam is neither an emulsion nor a mixture. It is an aggregate of intermetallic compounds.

Mercury is the only metal that is liquid at room temperature, and it evaporates at 20 degrees. However, oxidation of mercury lowers its evaporation rate by a factor of 1000. If an amalgam were a mixture, mercury would evaporate quickly at body temperature. However, the evaporation rate of mercury from amalgam is over four million times lower than unoxidized liquid mercury and 1.6 million times lower than if amalgam were a mixture.

People have been concerned about mercury release from the beginning of amalgam use. In 1972, John McNerney developed a mercury vapor detector, and the first demonstrated release of mercury from set amalgam was done in 1979 by Gay, Cox, and Reinhardt. The vapor detector became the Jerome mercury vapor detector. However, the detector does not work the same as human breathing. Unless the device is used properly and with flow rates in mind, it will overestimate mercury. Other factors, such as delay or certain foods, will also affect the reading.

There have been no prospective randomized trials to compare the longevity of amalgam versus composite. Retrospective studies show amalgam to last longer than composite fillings and that resin composites were significantly more likely to fail. The Casa Pia study published in April showed that after five years, the need for restorative treatment was approximately 50 percent higher in the composite group. Additionally, composite restorations are difficult where teeth touch adjacent teeth, and

even packable composites didn't show an advantage in proximal contacts in a 2001 study. Even the newest materials show greater wear at two years, and a comparative study by Evon Mjor et al, showed a higher incidence of secondary caries in composite than amalgam restorations. Composites also may contribute to plaque formation and higher cariogenic bacteria levels.

Glass inomers can also be used. However, despite the fact that the glass contains and releases fluoride, the leading cause of their failure is secondary caries, and an in vivo test showed no preventative effect by the device to protect adjacent enamel.

Composites have other biological risks: estrogenicity, cytotoxicity, and allergenicity. Additionally, the photocuring lights used pose some risk to oral cells, according to John Wataha, et al.

Heather Rosecrans, section Chief for the 510(k) program, gave an overview of device classifications. The medical device amendments to the Federal Food, Drug, and Cosmetic Act were enacted on May 28th, 1976. They defined a device, required classification of device types according to potential risk, and required pre-market review of devices for the first time. Pre-amendment devices were grandfathered. Post-amendment devices required pre-market review unless they were exempt. Pre-amendment devices stay on the market unless legal action is taken to remove them or they are classified Class 3. Pre-amendment devices include dental mercury, amalgam alloy, and encapsulated amalgam.

A manufacturer can market a pre-amendment device by making a 510(k) submission, demonstrating substantial equivalence, and receiving clearance. Device regulation and classification is risk-based. These three classes are Class 1, general controls; Class 2, general controls and special controls; and Class 3, general controls along with pre-market approval. Because amalgam alloy is classified in Class 2 and was a grandfathered device on the market prior to 1976, a new manufacturer's amalgam alloy that is determined to be substantially equivalent would also be classified into Class 2 through that 510(k) review process. Advisory panels make recommended classifications or reclassifications to the FDA. New information can lead to reclassifications or to devices being removed from the market. Only one device has been banned, implantable prosthetic hair fibers, because the benefit did not outweigh the risk.

Dental mercury, a device composed of amalgam alloy and the restoration of a dental cavity or a broken tooth was made Class 1. Amalgam alloy, a device that consists of a metallic substance intended to be mixed with mercury to form filling material for treatment of dental caries is a Class 2 device. Because they are used together, the combined class is Class 2. FDA has cleared 75 510(k) submissions for dental amalgams as Class 2 devices. In 1993, the Dental Products Advisory Panel recommended that dental mercury be up-classified to Class 2. In 2002, FDA proposed regulations to place all dental mercury devices in Class 2 and proposed a special controls guidance document, consensus standards, labeling requirements, and labeling recommendations. This final rule has not been issued yet.

Dr. Burton opened the floor for questions. Dr. Aschner asked for the definition of a medical device. Ms. Rosecrans said that a device does not rely on a chemical action and does not have to be metabolized to achieve its purpose.

Dr. Goldman asked the difference between dental mercury being Class 1 requiring a 510(k) and amalgam alloy in class 2 with a 510(k). Ms. Rosecrans said that the difference is that a Class 2 device requires special controls. A change in formulation could constitute a significant change and would require a new 510(k) submission, and the FDA would look to see if new questions are raised or more information is needed.

Dr. Amar asked if any post-market surveillance was done by the FDA with dental amalgam. Ms. Rosecrans said that dental amalgams do not have a required post-market surveillance. However, there is the medical device reporting process and adverse event reporting processes that are a general control for all devices.

Dr. Fleming asked what the effect would be of making amalgam a Class 3 device. Ms. Rosecrans said that after the device had been reclassified for 30 months before a PMA could be called for, and every firm marketing the device would have to file a PMA to stay on the market. Until then, it is a Class 3 device requiring 510(k), and the products would stay on the market until the PMA is denied.

Dr. Honein asked about the obstacles to moving dental mercury from Class 1 to Class 2. Ms. Rosecrans said that it was made Class 1 in the 1970s. The Panel recommended up-classifying in the 1990s, and the notice went into the Federal Register in 2002. There have been many comments, and this meeting is part of the process, especially public comment.

Dr. Arthur Conn of Health Canada spoke on the scientific basis for the regulation of dental amalgam in Canada. In Canada, the relevant regulations are administered by the Medical Devices Bureau. Most of the review work was done in the 1990s, and since the mid-90s, the primary activity has been monitoring the safety of dental amalgam. There have been two applications for dental amalgam since 2000. One was refused and the other approved. Health Canada classifies its devices into four classes, of which Class 4 is the highest risk. Dental amalgam, encapsulated amalgam and dental mercury are Class 3 medical devices. In Canada, all devices are judged independently in their premarket review documents, and there is no 510(k) type process.

Safety and effectiveness in Health Canada is a blend between the premarket review of objective evidence, post market surveillance, and audits. Health Canada does not have a guidance document or policy on dental restorative materials. Instead, manufacturers are required to provide evidence of safety and effectiveness. Health Canada recently published "Mercury: Your Health in the Environment, a Resource Tool." A Stakeholder Review Committee met in 1995 and made the following recommendations. Dental amalgam does contribute detectable amounts of mercury to the body, but there was no evidence that it was causing illness. It was recognized that mercury crosses the placental barrier, and it was advised to avoid procedures involving amalgam in pregnant women or individuals with renal impairment. For environmental reasons, less mercury should be used. Although there is no evidence that dental amalgam contributes to immunological, neurological or kidney disease in human populations, there is evidence that mercury exposure from all sources is more significant to individuals with

those problems; dentists and physicians should be aware of this in their choice of dental materials for these patients.

An internal report provided to Health Canada attempted to recommend a tolerable daily intake for mercury from dental amalgam, but the overall data was not considered adequate or reliable to permit an estimate of a tolerable daily intake, and the committee concluded that there was no evidence that the wholesale removal of existing amalgams was justified. Health Canada's current position is that the evidence does not indicate that dental amalgam is causing illness; however, it is a good idea to reduce mercury where practical. Non-mercury fillings are recommended in children's primary teeth, pregnant women, those with hypersensitivity, and those with renal dysfunction. They do not support removal of amalgams except for those with hypersensitivity and for those who are already having a filling repaired or replaced. Dr. Conn estimates that more than half of the fillings in Canada are amalgams. Their use is decreasing, as in the US, but regulatory activity has been limited. He said that Health Canada's position is identical to Dr. Mackert's position.

Dr. Goldman asked whether the recommendation for pregnant women was for all women of childbearing age or just for women who are actually pregnant. Dr. Conn said that it was just for pregnant women.

Dr. Amar asked about the 1996 position paper's conclusion, identified no impairments or evidence of mercury but alerted the public to potential risk anyway. Dr. Conn said that there was a great deal of conflict in the paper, and the general idea is that it is wise to avoid overall exposure to mercury.

Dr. Amar asked about specific at-risk populations. Dr. Conn said that the scientific basis for the regulation of dental amagam does not show any contraindications, so no specific at-risk classes have been identified.

Ms. Cowley asked about Dr. Conn's allusion to mercury allergy. Dr. Conn said that he had no clinical experience with it but understood it to be a local gingival reaction.

Dr. Diamond asked about other initiatives in Canada to reduce environmental exposure to mercury. Dr. Conn said that the Ministry of Health has a standard for managing dental waste. Most dentists now have amalgam separators.

Dr. Taylor asked about post-market surveillance. Dr. Conn said that there is no requirement for post-market surveillance except for mandatory problem reporting.

Dr. Zuniga asked about dental regulation in Canada. Dr. Conn said that it is regulated at the provincial level.

Dr. Lennart Philipson of the Medical Products Agency and Linkoping University in Sweden presented on the use of dental amalgams in Sweden. In Europe, medical devices are regulated under the New Approach Directive. There is no pre-market approval process for medical devices, but there is post-market surveillance. The manufacturer is responsible for the function and safety of the product. Medical devices are classified 1, 2(a), 2(b), or three. Dental amalgams are class 2(b). The device, packaging, and labeling carries a Z mark that identifies the notifier body and indicates that the product is suitable and safe for use.

In Sweden, dental amalgam use is down dramatically. 980 kg of mercury was sold for dental use in 1997, 100 kg in 2003. Six percent of fillings being installed in 2005

were amalgams. The Swedish national health insurance program does not cover amalgams. The possible health impact to patients and dentists has not been ruled out, so the country is trying to reduce the use, though there is no scientific clinical data demonstrating a connection between the use of dental amalgams and medical problems. Sweden is introducing a complete prohibition of mercury in 2007 for environmental reasons, though dental amalgams will be allowed in exceptional cases in hospital-based clinics. The National Board of Health and Welfare is putting new research into health problems associated with dental materials and has commissioned a national register for health effects related to dental materials.

Dr. Fleming asked whether Sweden had something similar to Norway's dental biomaterials adverse action unit. Dr. Philipson said they did not, but that may be the reason for the new register.

Dr. Olson asked what the adverse events were, other than hypersensitivity. Dr. Philipson said that the register is not yet producing any information he can distribute.

Dr. Taylor asked about the weight of restorations being used as a measure. Dr. Philipson said that was the measure he had. The data referred to metal sold by distributors of dental albumin.

Dr. Rizzo asked about the government's not paying for mercury fillings despite the lack of evidence. Dr. Philipson said that there is no threshold for the precautionary principle. The action was made based on a suspicion of a problem. Data from the register will guide future actions. Dr. Diamond commented that the centralized medical system in Sweden offers an opportunity for trend analyses.

Ms. Cowley asked how the registry would work and who would do the reporting. Dr. Philipson said that not everything has been decided yet. Dr. Taylor asked about including exposures in the registry. Dr. Philipson said that the registry is still under design, and not by him.

Dr. Amar asked what concerns had led Sweden to ban mercury and what equivalent alternatives are being used. Dr. Philipson said that he did not know all of the environmental concerns and agreed that the replacement fillings were not as durable.

Dr. Li asked what exceptional cases would lead to amalgam use and about potential safety concerns regarding other materials. Dr. Philipson said that recommendations on what is exception have not yet been written. He was not part of any discussions on new dental filling materials. In Europe, it is the duty of the manufacturer to show safety and effectiveness.

Dr. Richard Canady of the Office of the Commissioner of the Food and Drug Administration presented on the U.S. Public Health Agencies' evaluations relevant to dental amalgam prior to 1997. The US Public Health Service evaluated the safety of amalgam in 1993 and 1997. The EPA developed a reference dose (the level likely to not cause appreciable risk of deleterious effects over a lifetime) for inorganic mercury in the late 80s and one for mercury vapor or elemental mercury at the same time. In 1997, EPA gave a report to Congress about air quality that also addressed mercury reference dose levels. The study looked briefly at amalgam exposure. The ATSDR (Agency for Toxic Substances and Disease Registry) prepares peer-reviewed toxicological profiles on environmental contaminants. Mercury was done in the late 80s and updated in 1990,

1994, and 1999. The profile included a MRL (minimal risk level), which is similar to a reference level and is based on the same studies, most notably Fawler et al's 1983 study, which showed the lowest dose effect at 26 micrograms per cubic meter of air. EPA and ASTR converted the times, EPA to a 40 hour work week, ASTR to a 24 hour day, seven days per week. They then divided the converted exposure levels by 30 to protect for uncertainty. This resulted in EPA having a reference concentration of .3 micrograms per meter cubed and ATSDR having .2.

The US Public Health Service did one analysis and one update utilizing and including several agencies and academia. Their 1993 report, which covered 119 studies, concluded, "The current scientific evidence does not show that exposure to mercury from amalgam restorations poses a serious health risk in humans, except for an exceedingly small number of allergic reactions." One of the findings in the report looked at how much exposure is received by having amalgams. Exposures from amalgam was set at 1 to 5 micrograms per day. Assuming that 15 meters cubed of air is inhaled per day, the exposure rate is between .33 and .066 micrograms per meter cubed. The 1997 update concluded that the data does not support claims that individuals with dental amalgam restorations will experience adverse events.

Dr. Dourson asked if studies were done to better characterize the 1-5 microgram range. Dr. Canady said that the White Paper addresses that.

Dr. Goldman asked why the uncertainty factor was 30 and why studies focused on effects on children but not on the fetus. Dr. Canady said that the uncertainty factor was so high because Fawer's number was an adverse event number. Also, the high factor is supposed to control for sensitive populations.

OPEN PUBLIC HEARING

Co-Chairman Burton opened the floor for the first open public hearing, making the speakers aware of the time limits and methods of submitting written testimony. He urged all speakers to disclose any relevant financial relationships. .

Linda Brocato explained that she has been a victim of mercury poisoning for nearly 30 years, due to fillings put in her mouth when she was a child. The symptoms, including headaches, dizziness, numbness, loss of balance, and weakness, appeared in 1977 when she was 27. After many misdiagnoses and mistreatments, she had her amalgam fillings removed. Within two weeks, she started to get better, and her condition has steadily improved since. She was concerned that patients are not told that silver fillings contain mercury.

Charles Brown, Esq. of the National Council of Consumers for Dental Choice, an organization determined to abolish mercury dental fillings, said that his organization, together with two partner organizations, has filed a petition with the Commissioner to ban mercury fillings for pregnant women. He said that the application of amalgam results in a release of mercury into the body that is transferred to a fetus. CDC calls it a major exposure, as does the USPHS. There are suitable replacements for mercury fillings, and all modern dentists are familiar with them. Since there is risk with no benefit, banning them in pregnant woman should be an easy decision. Mr. Brown spoke of corruption and deception, including a gag rule on mercury and pay-for-endorsement schemes, by the

ADA, which supports amalgam. He urged the panel to keep in mind that the age of a device is not an indication of safety and that keeping amalgam would represent a social injustice when poor people receive mercury fillings. He also urged that silver fillings be called mercury fillings, since they are 50 percent mercury.

Dr. Amid Ismail of the University of Michigan spoke on behalf of the ADA. The Council on Scientific Affairs is charged by the ADA with responsibility for advising on safety and effectiveness of dental materials, among its other duties. The council follows the literature and makes assessments, which are updated whenever new information appears. The Council consists of ADA members with scientific expertise. It is a rotating membership. The Council's opinion is that dental amalgam is safe and effective. There is no association between dental amalgam and adverse health effects, except for allergies. It is a valuable device and should remain an option of patients and dentists, especially since it is the most effective device in large or deep fillings and in back teeth. It is also the only material that can be used in a wet environment. Amalgam is cheaper, lasts longer, and works better than the alternative products.

Dr. Ronald Zentz, spoke on behalf of the ADA. The ADA relies on the Council on Scientific Affairs to provide guidance, including guidance in the safety and effectiveness of dental materials. The Council promotes research to gather data to make the best-informed choice. ADA does not advocate specific restorative materials. Rather, it advocates a diversity of materials. The best and latest scientific evidence indicates that dental amalgam is safe. An amalgam trial in children was published in JAMA in April.

No adverse health affects were found. Two new clinical trials have compared overall health effects in children treated with amalgam to those treated with resin. The scientific community considers amalgam safe and effective, as does the ADA, WHO, FDA, CDCP, and NIH. However, amalgam use is declining, mostly for aesthetic reasons. Exposure to amalgam cannot be compared to an exposure to mercury, since the amalgam is a stable intermetalic compound. The mercury is not free or readily converted to methyl mercury. At present, there's no direct restorative material that works as well as amalgam for large fillings in the back teeth or in very deep fillings below the gum line. Alternatives are often less effective in these situations, especially in the wet environment.

Dr. Dourson asked about amalgam in the context of overall exposure. Dr. Zentz said that it was that component is lower. Also, elemental mercury and methyl mercury are not comparable concerns.

Dr. Goldman asked to see the ADA's material on which fillings to choose. He also asked if the ADA tracked adverse events. Dr. Zentz said that the ADA refers callers with events to the FDA.

Kathleen Nelson is a mercury poisoning survivor. She said that deciding not to implant mercury inside of patients should be an obvious choice. She applauded the FDA for its warnings about mercury in fish and for holding the hearing. However, she found the warning inconsistent with the dental implantation of amalgams. She discussed her personal experience with the illness, its misdiagnosis, and its eventual treatment by Dr. Kendall Stewart, who had the mercury fillings removed and chelation done. Her condition improved dramatically.

Dr. Joel Berg of the University of Washington spoke on behalf of the American Academy of Pediatric Dentistry (AAPD), which testifies to dental amalgam as a safe material. AAPD sponsored a consensus conference in 2002, at which the consensus statement read: "The dental literature supports the safety and efficacy of dental amalgam in all segments of the population. Furthermore, dental literature supports the use of dental amalgam in the following situations: Class 1 restorations in primary and permanent teeth; two surface Class 2 restorations in primary molars where the preparation does not extend beyond the proximal line angles; Class 2 restorations in permanent molars and pre-molars; and Class 5 restorations in primary and permanent posterior teeth." This recommendation is included in the AAPD guidelines on pediatric restorative dentistry. Amalgam's properties, such as ease of manipulation, durability, relatively low cost, and reduced technique sensitivity compared to other restorative materials have contributed to its popularity. Aesthetics and improved tooth color restorative materials, however, have led to a decrease in its use, not any valid evidence that the device is unsafe. Recent studies published in JAMA by Dr. Belliner and Dr. DeRouen show that children with amalgam fillings show no difference in neurological and renal function compared to the control group of children with composite fillings. The tiny amount of mercury released by amalgam does not affect health.

Dr. Dourson asked if the AAPD had studied mercury released during the placement. Dr. Berg said they had not.

Dr. Fleming asked the group's informed consent process in choosing a filling. Dr. Berg said that informed consent should come before all dental procedures, usually dealing with the longevity and size of the restoration.

Dr. Paul Gilbert, a practicing dentist and ADA member since 1962, said that mercury is a toxic heavy metal and should not be used in dentistry. Upon learning that mercury vapor comes off the fillings over 25 years ago, he became a mercury-free dentist. Dr. Murray Vinnie studied whether or not the mercury coming from the fillings was actually being absorbed by the patient, using a radioactive mercury isotope to track absorption in mammals. The ADA has ignored or attacked all such research. Mercury is poisonous at any dose level. Composite materials have improved with time. They are harder to place, but that only means more skill is required of the dentist.

Dr. David Kennedy summarized the International Academy of Oral Medicine and Toxicology's activities. Exposure and intake of mercury due to amalgam has been known for over 70 years. He challenged the idea that amalgam is a stable alloy, citing the Mazi study. In 1990, WHO determined that Dr. Mackert's dose estimate was too low and estimated it at 17 micrograms. Autopsies have demonstrated that the amount of mercury in human brains is proportional to the number of fillings in the teeth. Together, this shows exposure, intake, and body burden.

Citing the Casa Pia study, he disagreed with its findings that an eventual decline in mercury in the urine means reduced exposure. Rather, he counters that mercury has been shown to damage the kidneys, so decreased excretion does not mean decreased

absorption. He cited other studies: Dr. Summers' study linking fillings to antibiotic-resistant organisms, Dr. Frickholm's tracking mercury from rat fillings to rat fetuses, and Dr. Drash's finding mercury in human fetuses, where it was found to be twice as high in fetal blood as in meternal blood. It also is carried in breast milk.

There is a genetic subset of the population of nonexcreters. They have very low levels of mercury in their urine, fingernails, and hair because they do not excrete it. Porphyrin formation is found in another subset. He also said that amalgams are not beneficial devices because the process of filling the tooth weakens the tooth and leads to further procedures and gum disease.

Dr. Huggins summarized a study by the Adolph Coors Foundation, in which patients had amalgams replaced with composites. Many changes were noted, including a drop in cholesterol levels. Mercury binds with hemoglobin, dropping the blood's carrying capacity for oxygen. Removal of amalgams showed a decrease in hemoglobin simultaneous with an increase in oxyhemoglobin and an increase in urinary mercury excretion. It also led to a decrease in porphyrin in the urine and unusual proteins in the spinal fluid. He suggested that mercury binding to cells can cause an autoimmune response and malignant DNA.

Congresswoman Diane Watson has long advocated banning dental amalgam. When she was on the California legislature, she introduced the Watson Law, which required informed consent in the form of a fact sheet on the risk of amalgam fillings. It was passed in 1992, but it was 12 years and a recomposition of the General Board of

California before the brochure came out. In the US House, she co-authored HR-4011, the Mercury and Dental Fillings Disclosure and Prevention Act, which prohibits after 2008 the introduction into interstate commerce of mercury intended to be used in dental fillings.

In 2003, the DC Fire Department and HAZMAT units responded to a mercury spill at Ballou High school. Due to a 250 ml spill, the school was closed for 35 days. Over 200 homes were tested for contamination. The total cost of the clean-up was $1.5 million. In 2005, an improper disposal at Cardoza high school led to the school being closed for over a month and another costly cleanup. FDA has banned mercury in disinfectants, thermometers, and all veterinary products. Other countries are moving to limit or phase out mercury fillings. It is common knowledge that it is a dangerous substance.

She said that FDA is allowing the sale of amalgam despite that it is not proven safe, is not properly classified, and is not properly disclosed to the patients as to its composition and risks. Prominent legislators have written to the NIH Director on this issue and are holding hearings into the issue. Other agencies, including the CDC and USPHS, have spokenout on the issue. She urged FDA to ban amalgam as it has banned other mercury-containing products.

Dental offices are a prime source of mercury pollution, and dental procedures demonstrate that the material is considered dangerous to the dentist. Fewer than one in four Americans even know amalgam fillings contain mercury, but upon being informed, the majority would prefer a nontoxic alternative. Informed consent is not happening.

Nontoxic alternatives do exist. However, they are more expensive, so poorer people continue to receive mercury. The NAACP and the National Black Caucus of state legislators have endorsed legislation to protect children and pregnant women from mercury fillings. Although the use is dying out, it is important to move forward and prevent further health risks.

FDA must immediately insist that the public be told in advance of placement that amalgam is 50 percent mercury, it constitutes an exposure to a neurotoxin, and alternative fillings are available. The FDA has a legal duty to conduct an environmental impact study of dental amalgam before it classifies the material. Makers of amalgam should have the burden of proving it is safe. The FDA must make sure that burden is taken up. FDA must also ban the use of the product in children, pregnant women, and people with kidney disease, mercury hypersensitivity, or braces.

Sara Moore-Hines, a Pennsylvania psychotherapist, described her experience with dental amalgams and mercury poisoning. In 1996, she had four mercury fillings repaired. She got sick within two months. The symptoms included depression, flu-like symptoms, hair loss, and memory loss. Though mercury did not show up in her blood test, her condition worsened over the next four years. A DMPS urine challenge in 2000 indicated a high mercury level in the body. Her amalgams were removed and a cavitation surgery was done to remove mercury that had leaked into the jaw bone. This was followed by a detoxification program. Her condition improved as her mercury levels decreased. She said that there is no effective prediction of who will be sensitive and who will not and urged the FDA to take steps toward informed consent and education. She pushed for an

independent committee to review the research and for the FDA to abolish the fillings as soon as possible.

Dr. Bruce Hutchinson, a local dentist, said that the use of amalgam has decreased with time for cosmetic reasons. He felt that there are situations in dentistry that require amalgams, such as when a tooth cannot be kept dry. Amalgams are also more durable than composite fillings. Taking the option of amalgams away could, in some cases, result in a huge cost difference. If he thought amalgam was dangerous, he would stop using it, but he has not been told it is dangerous.

Dr. Nairn Wilson spoke for the Academy of Operative Dentistry, which says that amalgam is safe and effective for the restoration of teeth, though a small number of people have a localized allergic reaction. Available scientific information supports the safety, as do statements from the WHO and the World Dental Federation as well as scientific reviews by Clarkson et al in the New England Journal of Medicine and Brownwell et all in Toxicology Review. The AOD endorses the ADA's position and agrees that there is no justification for discontinuing amalgam use as well as the Council of European Dentists' similar resolution. AOD acknowledges the risk to health personnel and endorses proper hygene in application and the use of equipment for proper waste collection. AOD further acknowledges that adverse reactions occur and dentists should be alert to these rare occurrences and supports continued monitoring of all dental restorative materials. The AOD urged the Panel to focus on the science.

Dr. Vincent Mayher, President-elect of the Academy of General Dentistry, said that the decision of using amalgam or not should come down to the patient and the dentist. As a practicing dentist, he relies on articles in peer-reviewed journals and credible government entities for guidance. To ignore the determinations of the medical establishment would be to subject his patients to unscientific care. The institution has validated the safety of dental amalgam. However, he stresses the importance of the patient making an educated decision. There are always alternatives to amalgam, but the alternatives are often less effective or more expensive. He emphasized that amalgam may release a small amount of mercury but that the danger is in the dosage. It is important to know what the toxicity level is. Best management practices address handling and disposal issues.

Dr. Milton Marshall, a toxicologist and biomedical scientist, spoke for the ADA. He said that the mercury in amalgam is elemental mercury, HgO. Mercury can be released by amalgams, but the inhaled dose is small. The majority of inhaled mercury diffuses across the alveolar membranes and is retained by the red blood cells in the pulmonary system. The mercury oxidizes and is retained by the red blood cells. The majority of red blood cells bonded to mercury is secreted in the feces. Only a small amount of mercury is available to interact with other tissues. Chronic exposure to elemental mercury is best measured by monitoring urine mercury levels.

Occupational exposure is the most promising source of data. Urinary mercury levels in dentists with occupational exposure to dental amalgams are much lower than those seen in persons with occupational exposure in the core alkali industry. He cited reports on dental amalgam, including one published by the Life Science Research

Organization, which concluded that no adverse health effects were associated with amalgam use other than occasional allergic reactions. Long term use of nicotine gum, intense chewing, and more than 20 amalgam surfaces resulted in urinary mercury levels that approached occupational exposure. Occupational exposure levels did nto indicate adverse effects. Neither occupational exposure nor dental amalgam studies provided sufficient information to support the hypothesis that mercury exposure at levels absorbed from amalgam restorations caused an adverse effect on renal function. There was insufficient evidence to support an association with dental amalgam and development of autoimmune diseases. Case reports and studies of immune function demonstrated a localized allergic response in some individuals. Insufficient evidence was published in this time period to support or refute the hypothesis that elemental mercury contributed to adverse pregnancy outcomes.

Carol Ward, Vice President of DAMS International, is a mercury toxicity survivor who described her experience. After months of no diagnosis, she found a nutritionist who diagnosed the problem. Her symptoms included depression, equilibrium problems, repeated infections, dizziness, urinary and kidney infections, digestive disorders, memory loss, low thyroid, and visual field problems. After the fillings were removed and 20 days of BAL injection therapy, her condition improved. She pointed out flaws in the children's amalgam studies. DAMS holds the position that mercury amalgam fillings are inherently damaging and children are unwittingly exposed to this damage and effects that may not appear until later in life.

Dr. Emanuel Finn spoke for the Association of State and Territorial Dental Directors, which supports the continued use of dental amalgam based on the scientific evidence and history of safe use. The issue affects access to healthcare. Expressing sympathy for those who testified, Dr. Finn felt that the only safe thing is to follow the current science.

Angela Kilmartin of the British group, Patients against Mercury Amalgams, discussed her experience with mercury poisoning from dental amalgams. After the removal of her fillings, her symptoms went away and the mercury was excreted through her feces. During chelation, she was as high as 170 units per kilogram. Ten years later, she was at 3.7. An extracted tooth was taken to Cambridge University, and it is still releasing mercury. She stressed that the inhalation of mercury, a neurotoxin, is hazardous, especially to the brain. She also showed the electric effects of the fillings. Mercury vapor concentration is connected to the number of amalgam surfaces.

Teresa Pichay of the California Dental Association, expressed the CDA's support for the continuing use of dental amalgam based on the lack of definitive evidence linking amalgams to systemic illness. CDA has been challenged on dental amalgam by Rep. Watson, the Department of Toxic Substances Control, and Proposition 65, which requires public notification of almost any exposure to potentially hazardous materials. In every instance, the CDA relied on the 1993 and 1997 USPHS reports and the 1999 ATSDR profile on mercury.

Jessica Kerger discussed her experience with mercury toxicity. She has been declared completely disabled by Social Security, diagnosed with Alzheimer's, and told she had less than two years to live. Her condition has improved as a result of chelation therapy and glutathione, which helps take mercury out of the body. She is the plaintiff in a case against the ADA, the Ohio Dental Association, Johnson & Johnson, and Densbly & Densbly. Her problems worsened within a week of having a root canal done by drilling through an amalgam filling.

Marie Flowers described her experience with amalgam fillings and mercury toxicity. She received her fillings at 12. Until she was 46, she had no symptoms but three miscarriages. By then, she had 11 mercury fillings and her first neurological symptoms, which took 34 years to develop. Her neurologist had no definite diagnosis for her, and while she was prescribed prednisone, she broke a filled tooth while on vacation. A dentist patched the tooth, causing oral galvanism, which caused a faster leakage of mercury. Her dentist knew about her prescription, and she described to him the symptoms she was experiencing, but he did not recognize the problem. He put a crown on top of the tooth, resulting in increased galvanism and increased leakage.

She developed Lhermitte's phenomenon and developed food allergies due to mercury toxicity in the brain as well as other neurological symptoms. When she was tested for mercury, as a poor excreter, her tests were not high. She pointed out that there is no safe dosage for mercury and stressed that mercury toxicity is not a matter of allergy or hypersensitivity. It is poisoning.

Robert Reeves spoke on behalf of the American Academy of Oral Medicine and Toxicology. He said that dentists using amalgam are put in a bad position because the labeling on amalgams gives warnings about side effects similar to those described by many of the witnesses and the FDA has said that mercury can accumulate, leading to side effects. However, the ADA has a gag rule that keeps dentists from discussing the potential harm. Because most doctors are not trained in toxicology and medicine is so disconnected with dentistry, diagnosis is often difficult.

Dorice Madronero spoke against dental amalgam, citing the New York mandate that mercury separators be installed at all dental facilities. She opposed looking at the issue in a cost/benefit paradigm, considering the environmental hazards and the hazards to health. Citing the FDA's 1993 report on dental amalgam, she said that mercury exposure should be minimal. She discussed her two miscarriages and their connection to the drilling out and replacement of dental amalgam shortly before a miscarriage.

Dr. Rebecca Painter, a general internist in private practice, discussed her experience treating 85 patients with amalgam removal. She submitted letters from 25 of those patients. She noted that aspirin was a pre-amendment drug but there were studies done to prove safety and efficacy. Amalgam has not been well tested. She submitted a list of over 100 symptoms that have improved with the removal of dental amalgams, 33 percent of them neurological. She stressed that precedent does not necessarily mean safety.

Dr. William Raymond King III, DMD, discussed his experience with an aortic aneurism he had during a heart surgery. As a dentist, he had long been exposed to mercury, and a 1976 paper connects chronic low level inhalation of mercury vapor to aortic aneurism. The process of removing mercury fillings releases mercury into the air, which is inhaled by the dentist, patient, and assistant. He submitted data showing that patients are being exposed to mercury. He disagreed with Dr. Machert's assessment of the sensors. He said that there is no reason to put amalgam in a child's tooth. He pointed out that EPA has banned other products, such as phenylmercuric acetate in latex paint, for much lower concentrations of fumes than amalgams release.

Johann Werle, who works for Consumers for Dental Choice but came to speak for himself, stressed that amalgam is the only mercury-containing device that is intentionally implanted into the human body. He pointed out that although the labeling lists the ingredients and warns against use in hypersensitive populations, patients do not see the labeling, and the FDA has not indicate against pregnant women, children, or patients with renal failure. He said that the controvercy around the fillings should at least lead to informed consent and meaningful debate. He said that the substantial equivalence determinations were faulty, since Section 872.3050 does not define amalgam allow as containing mercury.

Kelly Gallagher, a cancer survivor and documentary film maker, suggested that her 17 fillings may have been connected with her Hodgkin's Disease diagnosis. She played video footage on the mercury debate. She said that she had seen a lot of contradictions as

she has been working on this project and hoped that FDA would be the hero at the end of the movie.

Dr. Nathan Fletcher of the National Dental Association said that there is more significant human experience with amalgam than with any other restorative material, and it is safe and effective. However, the NDA supports efforts to continue studying amalgam and developing alternative materials. He pointed out that in urban centers amalgam is often the only choice, due to cost and Medicaid coverage, and that in children who will not sit still, alternative materials would be impossible to place.

Clinton Zimmerman said that amalgam is not an alloy but an unstable mixture with vapor pressure, as well as the number one source of elemental and methyl mercury in humans. He shared his experience of mercury poisoning from a filling. He said that the ADA makes proclamations of the device's safety but brings no proof and that the exposure studies were mischaracterized in order to mislead the public. Studies have shown theoretical exposure from amalgam to be several hundred times the normal exposure. He went on to say that amalgams and oral conditions vary and an upper level to exposure cannot be set. Copper increases exposure, and surface bacteria can cause liquification of surfaces and release of methyl mercury. He said that methylation is documented but is purposely ignored by dental authorities.

Dr. Steven London of the College of Dental Medicine at the University of South Carolina spoke for the American Dental Education Association and the American Association for

Dental Research. He said that the Committee withdrawing support for amalgam would harm dental training. He said that any decision should be based on science and that the science is that it is safe and effective. He cited a study on children showing no adverse effect, which was published in JAMA in April of 2006. He said that, although the use of amalgam is decreasing, it still has a place in treatment. He said that the White Paper corroborates the AADR's official position on amalgam.

Sue Ann Taylor with the Consumer Choice in Dental Care Project said that she had mercury poisoning that abated when her amalgams were removed. Her son developed mental problems after the placement of nickel posts for tooth restoration. When they were removed, the problems abated. She stressed the importance of examining all materials for biocompatibility for everyone.

Anita Tibau of Ugottawanna Productions showed video footage of Representative Burton questioning Dr. Feigal on amalgams. She hoped that the FDA would at least bann the product in pregnant women.

Dr. Paul Connett, said he studied interaction of metals with biological systems, and his advisor dies of mercury poisoning. He also pointed out that people cremated with amalgams in their teeth would release mercury into the environment. He said that it is important to restore the public trust in the FDA. He felt that his studies of fluoride parallels the mercury issue. He said the CDC has been unduly influenced by the ADA on

water fluoridation and that the EPA's safety margin was too small. He emphasized looking at all the evidence and employing the precautionary principle.

Dr. Isabella DeNede spoke for the European Commission. In Europe, dental amalgams are class 2(b) devices, meaning the manufacturer has to comply with essential requirements: the device must not compromise the health, clinical condition, and safety of patients and the safety of the health of the users; and any risk associated with their use should constitute an acceptable risk when weighed against the benefits to the patient. This is reviewed by the notified body. There is a trend toward decreased use in the member countries, varying by country. Some countries have introduced specific recommendations to use alternative fillings for specific patient groups. The European Commission convened an expert group to review evidence on amalgam in 1993, and it found no reason to restrict the use. Recently, though, there has been an emphasis on limiting mercury exposure. The Commission will get the opinion of the appropriate scientific committees and review the evidence on mercury and alternatives before making a risk management decision or formal recommendation. Mercury is listed as a hazardous compound, and most member states have laws for the disposal of amalgam.

Dr. Andrea Brockman discussed her experience as a dentist. In dental school, she learned that discussion of mercury dangers is discouraged. She developed mercury poisoning and had a miscarriage in dental school. Although she did not use amalgam fillings, she did drill them out, and when she did have a child, he had high levels of mercury in him and developed symptoms.

Karen Palmer read her two submitted letters into the record. Ms. Palmer is a former dental assistant who developed mercury poisoning. She stressed that mercury poisoning is not an allergy and urged that informed consent be made mandatory. Mercury vapor goes through gloves and masks, and most offices have insufficient ventilation. She urged the FDA to take on the ADA.

ADJOURNMENT

Co-Chairman Kieburtz thanked the participants and adjourned for the day at 4:59 p.m.

I certify that I attended this meeting of the Dental Products Panel and Peripheral and Central Nervous System Drugs Advisory Committee on September 6, 2006 and that these minutes accurately reflect what transpired.

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Michael E. Adjodha, MChE
Executive Secretary

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LT Darrell Lyons, BSN, RN
Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

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Richard Burton, DDS
Chairman

_____

Karl Kieburtz, MD, MPH
Chairman

Summary Prepared by

Eric M. Hendrixson
Neal R. Gross & Company
1323 Rhode Island Ave, NW
Washington, DC 20005
(202) 234-4433
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