SUMMARY MINUTES

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

September 7, 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

Co-Chairman Burton called the meeting to order at 8:00 a.m. and Executive Secretary Adjodha read the conflict of interest statement into the record.

OPEN PUBLIC HEARING

Co-Chairman Burton opened the public hearing session, reminding the public of their opportunity to submit written comments.

Michael Bender, director of the Mercury Policy Project, discussed Mercury Girls, a Norwegian documentary on mercury-related complaints by dental nurses. Every time amalgam is prepared, mercury is released at high levels. After the documentary was aired, 400 women, all former dental assistants, called the television station reporting miscarriages, severe bleeding, and many symptoms in their children. When the documentary was shown in Denmark, 1650 dental nurses called the trade union with concerns. Norway and Denmark are working on a collaborative multiyear study on neurotoxic mercury effects on dental workers. Norway actively discourages amalgam use. Stressing precaution, Mr. Bender urged that the FDA ban mercury tooth fillings placement during pregnancies and that dental nurses be placed on paid leave during pregnancy. Dr. Rachel Obbard of the Mercury Policy Project played excerpts from Mercury Girls.

Michael Burke spoke on his wife's early onset Alzheimer's disease, which was diagnosed to have been caused by heavy metal toxicity. Mr. Burke felt that bioaccumulated

mercury vapor from mercury fillings over the course of many years is the primary causative trigger for Alzheimer's disease. He first pointed out that Alzheimer's does not occur in third world countries, where fillings are rare. A 1993 study showed that the risk of Alzheimer's increases in people with an APO-E4 gene. The cysteines in people with APO-E2 or APO-E3 are sulfur-based amino acids, so they attract, bind, and excrete mercury. The cysteines in APO-E4s do not bind well with mercury because a different amino acid is used. As a result, people with that gene bioaccumulate mercury without excreting it. The physiological changes that occur in the brain cells and neurons with Alzheimer's has been reproduced in the laboratory by low level mercury exposure. Mercury fillings carry an electric charge, and the higher the negative charge, the more mercury is being released. He said that mercury should not be used in medicine and dentistry because mercury is a strong neurotoxin with demonstrated adverse effects.

He said that the ADA was created because the original group, the American Society of Dental Surgeons, refused to use mercury. The ADA's position on the safety of amalgam is based on no evidence and mercury has been accepted due to the ADA's deceptive practices.

Dr. Howard Bailit of the University of Connecticut presented a six-year study on the economics of regulating amalgam restorations performed by him and sponsored by both the ADA and the CDA (California Dental Association). In 2004, they projected 166 million restorations, of which about 31 percent would be amalgams. For all groups and ages, amalgam use is declining by 3.7 percent per year. Estimating the financial impact of banning amalgams in children, women of child-bearing age, and the entire population,

the group concluded that a total ban on amalgam would raise the average cost by $52, result in 10 percent fewer restorations performed, and cost consumers $8 billion. Banning use in women and children would cost $4 billion, one billion for just children. This would result in people using fewer services, adversely affecting health and leading to increased health disparities. Because there is no evidence of amalgams causing ill health, he recommends not banning amalgams.

Dr. Boyd Haley, a scientist at the University of Kentucky, challenged the ADA's findings, saying that the vapor levels they claim would be undetectable. He's measured the levels coming off amalgams and asked why the FDA has not had an uninterested party test the mercury coming off amalgam. A study in JADA showed mercury in the micromolar range in the brains of Alzheimer's patients, a thousand to ten thousand times the level necessary to kill neurons. He demonstrated how neurons exposed to mercury vapor have the same biochemical photolabeling profile seen in Alzheimer's brains. Only mercury can do this. He also demonstrated mercury being released when a dental amalgam is soaked in water. Mercury is known to cause many other neurological disorders, and Dr. Haley concluded that a patient with many amalgam fillings will cross to Alzheimer's dementia quicker than one without. Mercury triggers elevated glutamine synthetase and creatine kinase inhibition, both leading markers of Alzheimer's. He explained that a genetic marker of susceptibility to Alzheimer's, EPO-E4, also indicates a lowered ability to remove mercury from the central nervous system. A mixture of genetics and mercury exposure is what leads to mercury in the brain and the subsequent

disorders. He also said that there is a correlation between idiopathic dilated cardiomyopathy and mercury levels and urged FDA to look further into mercury.

Dr. Pam Factor-Litvak, a professor of epidemiology at Columbia University, presented her research on mercury fillings. Her transportation was funded by ADA, but she was not paid to appear. She acknowledged that there is some exposure from fillings but questioned a causal relation between the exposure and adverse health effects. From 1997 to 2000, she conducted a cross-sectional observational study evaluating the potential harmful effects of amalgam restorations in otherwise healthy adults. 550 subjects, ages 30 to 49, with amalgams 10 to 20 years old were evaluated with a wide variety of tests, including cognitive, neurological, and urine tests. The results indicated no adverse associations between any of the measures of mercury exposure: urinary mercury adjusted for creatinine, number of total amalgams in the mouth and number of occlusal amalgams in the mouth, and any of our outcome variables.

David Laureems, a consultant to the American Association of Public Health Dentistry, said that there is no causal connection between dental amalgam and health problems. There is no evidence of harm and great evidence of benefit. Tooth decay is an important health problem in the US, and there are significant health disparities in dental care. Banning dental amalgam would raise the barriers to treatment and increase disparities.

Jay Grant spoke for the National Association of Dental Plans. The NADP relies on literature and professional experience to set dental benefit levels. Literature from the

FDA, CDC, USPHS, NHI, and AMA supports the efficiency and safety of amalgam fillings. It is the most effective material for posterior teeth and most common material covered by dental benefits. Composite resins may be covered for more visible teeth, but the materials cost 40 to 60 percent more. About 10 percent of dental claims are fillings, and the elimination of amalgam would increase the overall cost for dental procedures by 2.5 percent, over half a billion dollars per year. Eliminating cost-effective treatments such as amalgam fillings will cause premium increases, leading to fewer people having dental coverage.

Dr. Felix Liao, a mercury-free dentist, read from two of the letters his patients had written and submitted them into the record. A letter from Mary Huff described her experience of a multiple sclerosis misdiagnosis that turned out to be mercury poisoning. Her symptoms went into remission after amalgam removal and chelation. JT's letter described thirty years of depression starting with the application of five dental amalgam fillings. Upon the removal of her fillings, her depression lifted. Dr. Liao concluded that mercury-free dentistry is good medicine, amalgam use is bad medicine, and that mercury-free dentistry can reverse the adverse neurological effects of mercury.

Freya Koss shared her experience with neurological and other illness caused by mercury amalgam fillings. Her symptoms started manifesting one week after having a mercury filling drilled out and replaced. They included double vision, dropping eyelids, loss of equilibrium, and ataxia. After her neurologist gave her a series of misdiagnoses and discouraged by the lack of effective treatment, she researched her condition intensively

before she found symptoms and onset matching hers on the Internet, which lead her to research mercury poisoning. When she had her amalgams removed, her symptoms went away, but very slowly, and some symptoms still have not left her. She disagreed with the White Paper drafters' statement that the World Health Organization had never taken a position on amalgam, citing WHO's 1991 report that called dental amalgam the greatest source of mercury vapor to a patient. She urged the FDA to reclassify amalgam as Class 3, require informed consent, and give warnings. However, she said the best thing would be to ban mercury altogether.

Sandra Duffy of Consumers for Dental Choice said that the Committee is not limited to merely approving or tweaking the White Paper. She warned that FDA was trying to resurrect the 2002 proposed rule. However, that proposal is dead, and FDA cannot classify without a Committee recommendation. She urged the Committee to take up the issue, reclassify the device Class 3, and ban mercury fillings in pregnant women. She said that the FDA has failed to classify encapsulated amalgam, do an environmental impact study on it, or require proof of safety. Instead, it used an invalid substantial equivalence test, according to the Department of Justice. She said that the FDA was ignoring its legal duty because an assessment would lead to the discontinuation of the product and that the FDA was trying to limit the literature the Committee could see. Amalgams are not safe. They are not necessary, and Medicaid will cover alternatives. She submitted further documents into the record. She urged the Committee to ban mercury fillings in pregnant women.

Dr. Steve Markus, a mercury-free dentist, said he first learned the danger of mercury when he read the Vimy study in dental school. He considered the precautions taken in the storage of amalgam scrap. Outside the patient's mouth, amalgam was treated as a hazardous material. Inside the mouth, it was treated as perfectly safe. He determined that the ADA recommendations were inconsistent. He said that if sweeping changes were made in the field due to AIDS, they could be made for mercury sensitivity. He argued that amalgams are not cost-effective, since the cost estimates do not factor in treating the illnesses caused by the mercury. He also said that when used properly with rubber dams in place, placement of composite resins can be done in any situation, and the resins are durable. He urged the FDA to ban amalgams.

Karen Burns, a former dental assistant, shared her experience with mercury poisoning. She has been sick for eight years and still has elevated blood levels after 12 chelations. She urged the FDA to ban amalgams.

Though he works as a lobbyist, Dr. William Duncan, a former staffer for Congressman Istook, spoke as a private citizen. He quoted CDC director Julie Gerberding, who stated that mercury is a dangerous metal no one should have put in his or her. He addressed the mercury release rates from new amalgams, stating that amalgams emit much higher levels of mercury during the first few weeks than reported in the literature, in amounts much higher than FDA guidelines for exposure. The new, high-copper alloys release more than the old low-copper alloys. With so much effort and money going to mercury

avoidance, he urged the Committee to conclude that it should not be implanted, just as the FDA has concluded it should not be injected or used topically.

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John Rowe, who worked for the House Committee on Government Reform and Oversight and coordinated three congressional hearings on amalgam, felt that his seven amalgam fillings may have triggered his leukemia, which was diagnosed two years later. He expressed concern about the lack of informed consent, and the lack of discussion about alternative materials. The ADA gag rule came up constantly at the congressional hearings. Though ADA denies it, many state boards seem to enforce the gag rule. According to the Institute of Medicine, at least 60,000 babies are born each year in the US with the risk of learning disabilities due to mercury poisoning due to their mothers' fillings. He urged the Committee to take steps to protect babies.

Dr. Ernie West showed video footage of a discussion on mercury amalgams in pregnant women.

Dr. Burton thanked all of the presenters and closed the open session.

LITERATURE REVIEW

Dr. Mery Paule, director of the Division of Neurotoxicity, NCTR, gave the literature review. The review was to address recent concerns expressed by some members of the public related to adverse health effects of dental amalgam. In keeping with FDA's ongoing commitment to monitor the state of the science on the safety of dental amalgam,

the FDA's National Center for Toxicological Research was charged to prepare review of the state of the science regarding the potential health risk of mercury in dental amalgam.

The USPHS last reviewed amalgam in 1997. The purpose of the 2006 review was to determine whether peer-reviewed scientific information published since then changes the understanding of the risk. This review builds upon rather than duplicating previous reviews, so it focused on identifying peer-reviewed studies important to the comprehension of health risk for inorganic or elemental mercury, or to mercury in dental amalgam since 1997. Each of the identified studies was then to be critically reviewed. When appropriate, the review of another public health agency could be referenced. The report was to provide an overall assessment and summary conclusions, specifically what contributions peer-reviewed scientific literature published after 1997 has made to the understanding of mercury-containing dental amalgam and its potential risk to human health.

Other US Public Health Agencies have done work on the subject. The Agency for Toxic Substances and Disease Registry (ATSDR) formulated a toxicology profile for mercury in 1999, published a detailed peer-review evaluation, and established minimal risk levels. ASTR has undergone literature searches every year since. EPA conducted an Integrated Risk Information System (IRIS) literature review in 2000 for mercury vapor and inorganic mercury. They used the review to decide whether to update their health-based reference values used in environmental regulatory programs for mercury.

FDA’s review and strategy process was to identify relevant peer-reviewed articles published from May 2003 to May of 2006. This period overlaps recent reviews by the Agency for Toxic Substances and Disease Registry and coincides with the publication of

a 2003 World Health Organization document and the EPA's 2002 literature review. 911 citations were found in a keyword search, 200 requested for further assessment, and 24 of those were judged to provide the most significant new information. No study was excluded based on its conclusion. Previous government literature reviews provide health effects-based exposure reference values for mercury vapor and inorganic mercury. They compare reference exposure values in urinary mercury concentrations and are applicable to safety assessments of dental amalgam. The EPA reference concentration (RfC) and reference dose (RfD) and the Agency for Toxic Substances and Disease Registry's minimal risk level (MRL) are used to determine a safe level of exposure. Since conservatism is built in, these levels do not represent thresholds for toxicity.

The 1999 ATSDR MRL for chronic inhalation exposure to elemental mercury vapor is 0.2 micrograms per cubic meter, about 4 micrograms per day, approximately the general population exposure for dental amalgam, 1-5 ug per day. The 2005 update saw no new studies warranting an update, so they made no change. EPA's 2002 IRIS screening-level literature review did identify study data that could potentially produce a change in RfC, but after reviewing the data, no change was made in RfC or RfD. These levels remain unchanged through the present and are derived to be protective of human health, including sensitive subpopulations. They also ensure that FDA has not overlooked relevant studies.

FDA looked at a nongovernmental public health organizations' literature reviews as well. WHO's 2003 Concise International Chemical Assessment Document (CICAD) looked at human health effects of elemental and inorganic mercury, and was peer-reviewed by an international panel of experts. Estimated exposure from amalgam was

determined to be less than 5 ug per day in the US and Canada. The central nervous system is considered the most sensitive target to long-term exposure, and subclinical effects have been reported at workplace air concentrations greater than or equal to 20 ug per cubic meter. They concluded that a tolerable continuous intake for vapor is 0.2 ug per cubic meter.

FDA reviewed additional scientific literature on mercury toxicokinetics and exposure characteristics. Several studies demonstrated that background levels of mercury in urine for people with no amalgams ranged from .54 to 1.4 ug per g of creatinine; for people with amalgams but no occupational exposure, the range was less than one ug to about three per g of creatinine. For every ten amalgam surgaces, urine levels increased by .8 to 1.4 ug per g of creatinine in adults, less in children. About 70 to 80 percent of inhaled mercury is absorbed, and airborne levels of less than 10 ug per cubic meter are not accurately reflected in urine levels. One paper demonstrated that there is no large change in blood mercury levels after amalgam fillings are removed, not even years later. Fetal mercury exposure is greater than postnatal exposure, even with continued exposure to breast milk.

Studies on human exposures to mercury vapor and neurobehavioral outcomes showed that neuropsychological effects are the most sensitive endpoints at concentrations exceeding occupational exposure guidelines. Workers exhibited neurological deficits at the end of chronic exposure and had urine levels of 21 ug/g Cr, though the levels and deficits improved when tested five years later. Workers occupationally exposed to very high levels (100 to 200 times that of people with dental amalgams) have long-lasting effects on the peripheral nervous system function, though most measures showed no

residual effects and no findings of dementia or effects on cognitive function. No association has been shown between occupational exposure to mercury and congenital malformations. Dental professionals were studied as a groups working regularly with amalgam. One chelation study suggested that the body burden is much greater than indicated by pre-chelation urinary levels; urinary levels were ten time higher after chelation than before. Neurobehavioral deficits, including finger-tapping, hand steadiness, and visual discrimination, correlated with measures of recent or current exposures. However, other studies using the same testing of non-dental occupational exposures with higher Hg levels in the urine did not show those effects, and there were no non-dental controls built into the study, so there may be some non-mercury occupational exposure confounding the results. Studies looking at human genetic polymorphisms and interactions with urinary mercury levels failed to show a correlation between indices of long-term exposure and neurobehavioral outcomes; only current exposure showed an effect. Due to lack of proper control groups, the degree to which polymorphisms will affect response is still unknown.

Studies of amalgam exposures in human were reviewed. A study that followed children with amalgams for 5-7 years showed no adverse effects. Large retrospective studies of adults also did not produce data that supports adverse events. One study showed an association between amalgam and multiple sclerosis, but the rate of observation in the study was actually much lower than in the general population. A cross-sectional study showed no correlation between urine mercury levels and neuraxis endpoints. Other studies showed correlations between the number of amalgam surfaces

and decreased vibrotactile response. Other studies failed to connect mercury to low birth rates or Alzheimer's disease.

Studies in animals showed no fetal developmental toxicity until the levels were high enough to cause maternal toxicity. Exposure to high concentrations of mercury vapor during rat gestation did not cause significant adverse effects in the electrophysiological outcome of the rats when they were tested as adults. The high dose rates in the animal studies make them not comparable to human exposure.

Based on the analysis of the 34 peer-reviewed articles published since 2003 and the evaluation of EPA and ATSDR's reviews, FDA concludes that the literature since 1997 does not substantially change FDA's understanding of the health risk of mercury in dental amalgam.

Dr. Luster asked about the determination that urinary mercury is not a good indicator for exposure. Dr. Paule said that is true at low levels of ambient air concentration.

Dr. Amar asked about the search engine used for the search, commenting that using more than one engine might have widened the search. Dr. Paule said that only PubMed was used.

Dr. Dourson asked about the 5 ug per gram value. Dr. Paule said that 95 percent of those with dental amalgams fall below that number. Dr. Dourson further asked what was meant by the language "except for a rare allergic or hypersensitive reaction." Dr. Paule said that a number could not be applied but that the proportion corresponded to the high end of a bell curve. Dr. Ascher followed up on the question, asking about temporal

exposure. Dr. Paule said that levels may fluctuate over time and that most of the values he saw were not immediately after placement.

Dr. Goldman asked about fetal neurotoxicity, commenting that the mother and child seemed to have the same levels at birth and wondering where the effect level is. Dr. Paule said that there has not been enough research on that subject.

Dr. Fleming asked if FDA has, considering the variability of mercury levels in human brains in the studies, modeled the studies. Dr. Paule said that was not within his charge, which was to review the literature, though there would be a benefit to doing so. Dr. Fleming commented that the lack of emphasis on pharmacologic and pharmacokinetic aspects of mercury makes the White Paper deficient and further asked whether FDA was comfortable with urinary excretion as the most valid way to examine mercury levels. Dr. Paule said that the number of amalgam surfaces is the best measure, since it reflects exposure rates. .

Ms. Cowley asked who is having adverse reactions to amalgams. Dr. Paule said he could not identify or predict a specific population.

Dr. Taylor asked if the quality of the studies was considered in weighing the evidence. Dr. Paule said that the emphasis had been on inclusiveness and that the FDA had noted deficiencies in some reports but included them because they provided useful information.

Dr. Hughes commented on the variability of concentration in the urine. Dr. Paule agreed that there are populations with higher placement rates of amalgam. Dr. Hughes commented that the NHANES dataset is in the public domain, so it would be possible to fill in missing levels in some studies.

Dr. Rizzo asked if the discrepancy between effects of dental versus non-dental occupational exposure could be explained by the testing procedures in the different studies. Dr. Paule said that the tests were comparable, often identical.

Dr. Honein commented on an editorial mistake in the White Paper, then asked if there was a hypothesis as to what might be a confounding exposure in the dental professional group. Dr. Paule said he had no hypothesis but speculated that there are a number of chemicals all dentists work with that could be causeing the effects.

Dr. Goldstein commented that the charge to the Committee is to judge the adequacy of the White Paper and that the Committee has not been given sufficient information to reach a conclusion. Dr. Taylor followed up, asking if the quality of the previous reviews was examined and considered. Dr. Paule said that the reviews had been approved, so they were assumed to be good.

Dr. Kieburtz asked how WHO reached its value of 1 to 5 ug per day when both of the Swedish studies estimate 5 to 9 and an average of 12. Dr. Paule did not know.

Dr. Goldman commented that the included studies seemed to have been chosen for their usefulness in determining no observed effect levels and lowest observed effect levels, so they may not be the same as the inclusion criteria of the ATSDR and EPA reviews. Dr. Goldman asked for information on peak concentrations during actual procedures. Dr. Paule said that the data is not available. Dr. O'Brien followed up, asking about the levels found in dental labs and OSHA standards. Dr. Pauls said that none of the studies examined considered air mercury levels in the workplace.

Dr. Zero asked what is meant by sensitive subgroups and whether hypersensitivity is short term or chronic. Dr. Paule said that children, elderly, and the infirm are

considered sensitive, but hypersensitivity refers to allergic reactions, and there is no literature identifying or defining that subgroup. Dr. Olson asked if there were any studies on the effects of mercury on immunocompromised patients. Dr. Paule said that he had looked specifically for that kind of study and found none. Dr. Sacco asked Dr. Paule to identify other gaps in the literature. Dr. Paule said that he hoped the Committee would identify gaps, but he said that very long-term data, 10-30 years after implantation, is needed. Dr. Porter suggested that hypersensitivity is related purely to the ability of some patients to accumulate more mercury than others.

Dr. Luster suggested that the average urinary mercury levels may be misleading and asked about the range of mercury levels within the population. Dr. Paule said that the high end went up to 17 ug/g Cr, which was unusual. The proportion is that mercury goes up 1 ug/g Cr for every ten amalgam surfaces placed.

Dr. Fleming commented that symptoms do not seem to correlate to urine levels and asked if that indicated a retention phenomenon. Dr. Paule said that was not considered in his analysis. Instead he looked for a dose-related effect.

Dr. Diamond suggested the inclusion criteria, which tried to exclude patients with complex medical histories, may be excluding patients that might show hypersensitivity.

Dr. Klaassen asked if the studies differentiated the sources of the mercury in the urine. Dr. Paule said that most of the studies reported inorganic mercury levels.

Dr. Kieburtz asked if reviews by other governments were considered, since they seemed relevant. Dr. Paule said they were not, since it was not included in the charge.

Dr. Amar commented that the testimony shows that it often takes decades for symptoms to appear and weeks for the symptoms to subside after amalgam removal and

asked if the literature showed any similar events or analyzed similar timeframes. Dr. Paule noted that the literature does not show mercury levels falling by much after removal for long periods of time. The literature does not support the testimony.

Ms. Cowley asked what percent of the population will be hypersensitive. Dr. Paule said he did not know. She asked if the studies looked at the effects of mercury by sex. Dr. Paule said they did not.

Dr. Ascher asked if there had been studies on tin evaporation from amalgam or on a possible interaction between tin and mercury. Dr. Paule said he had seen no such study.

Dr. O'Brien asked about studies on the placebo effect. Dr. Paule said he had seen none.

COMMITTEE DISCUSSION

Dr. Alderson led the Committee through the discussion questions.

1) Based on the peer review of the scientific literature, the draft FDA White Paper, and, any other information, including the information you heard in the public session, please discuss the following topics, including any issues of quality, experimental design, or other attributes of the specific studies that may affect the weight that should be given to conclusions drawn from them:

1a) Please discuss the direct evidence, if any exists, supporting or refuting the occurrence of adverse health effects for mercury vapor release from dental amalgam devices.

1b) Please discuss the indirect evidence (e.g., extrapolation for higher dose studies and animal studies), if any exist, supporting or refuting a link between dental amalgam

devices and adverse neurological effects at the absorbed doses received from these devices.

1c) Please discuss the indirect evidence (e.g., extrapolation from higher dose studies and animal studies), if any exists, supporting or refuting a link between dental amalgam devices and adverse non-neurological effects at the absorbed doses received from these devices.

1d) Please discuss the indirect evidence (e.g., extrapolation from higher dose studies, animal studies), if any exists, supporting or refuting a link between dental amalgam devices and adverse effects specific to vulnerable populations such as children and pregnant women at the absorbed doses received from these devices.

The Committee's consensus was that the direct evidence, largely due to what is not in the White Paper and the presented materials, neither supports nor refutes adverse health effects. The studies do not support any finding of adverse effects from dental amalgam. However, the lack of evidence is not a refutation. Dr. Hughes added that at times, such as in the two pediatric randomized trials, it is debatable whether the results support or refute adverse health effects. Following the patients further out may yield clearer results, though the loss of fillings as primary teeth are lost complicates the question. Dr. Goldstein added that a study only answers the questions it asks, so unanswered questions remain. Dr. Goldman added that the studies could not detect very small subpopulations but that the studies were reassuring in the general population. Sensitive populations must be identified by a different method and studied. Dr. Goldstein added that the adequavy of the White Paper is unknown, due to questions of methodology. Dr. Burton commented that the various sections of question 1 were not so

much questions requiring answers so much as guidance on how to consider questions 2 and 3. The question was not brought to a vote.

Dr. Kieburtz restarted the discussion when he took the chair in the afternoon. Dr. Zero commented that many of the studies relied on urine mercury as an indicator, but there are doubts as to whether or not it is a valid indicator or body burden or exposure. Dr. Kieburtz noted the great variability in urinary excretion measures. Dr. Porter pointed out that the document does not note the fact that over 90 percent of mercury excretion is through feces. Dr. Kieburtz stressed that the question is whether the White Paper reflects the state of knowledge, not whether or not the state of knowledge is adequate. However, the FDA is interested in knowing what data gaps exist. Dr. Ascher said that urine excretion is the best estimation of inorganic mercury excretion, but it's not an adequate measure of body burden.

Dr. Dourson added that the EPA's safe dose estimates were intended to factor in sensitive populations. However, it is not clear that the adjustment is valid, since it is not clear that all the mercury in urine is coming from amalgams. Dr. Fleming responded that the literature uses a lot of probability and that "sensitive" and "rare" are not well-defined. Committee consensus was that one knowledge gap is an accurate measurement of the exposure burden with acute manipulation of and chronic exposure to amalgams; another is that there is no good measure of body burden. The chelation and animal evidence implies that there is a depot effect, so excretion does not necessarily reflect exposure. Mechanical disturbance from brushing and chewing is another unaddressed variable.

Dr. Luster expressed concern that the EPA and ATSDR reviews both used the same data set to reach their numbers and had different goals in mind from what the FDA

had. Dr. Goldman added that risk assessments can only be done for certain narrow risks, not the totality of risk. Ultimately, Dr. Zero said, the data does not show what will happen in an adult patient with a chronic body burden from various mercury sources.

Dr. Honein pointed out another research gap: fetal exposure. He asked about the standard of care in pregnant women. Dr. Fleming said that maintenance of teeth, which is emphasized during pregnancy, will result in an acute hit. Dr. Burton added that not only is dental care not discouraged during pregnancy but women often become eligible for Medicaid during pregnancy, so they tend to get a lot of dental care at that time. That makes exposure even greater during pregnancy than at other times. Dr. Amar said that the American Academy of Periodontology's protocols preclude third trimester treatment, except for in emergencies, and suggested that the Committee look at the literature to see if its been properly addressed, using more search engines this time. Dr. Burton pointed out that women often do not know that they are pregnant early on.

Dr. Goldstein said that dose levels are not binary but continuous and wondered at what rate risk increases as the threshold is approached. Dr. Ng noted that the studies excluded younger children, children with medical problems, and fillings on anterior teeth, which would bias the studies. Dr. Sacco said that the superiorities of amalgams over composites should also be considered. Dr. Zero said that, although there are times when it is difficult to use a composite, better composites are being made. Dr. Fleming said that experience and training make the issue moot.

Dr. Kieburtz directed the conversation away from knowledge gaps and back toward the questions. Dr. Hughes said that the studies were all about short term effects and that the question being addressed was long-term effects. Dr. Kieburtz quoted the

Swedish dental assessment: "At present, it may be considered unproven, but not excluded, that subclinical psychomotor function impairment caused by mercury is demonstrable in groups at the mean exposure level for amalgam bearers." He said that the Committee might come to the same conclusion. Dr. Porter agreed, citing the diverse levels in the cadaver study. Dr. Diamond concurred that statistical curves could be made but that the individual patient data was very disparate.

Dr. Li asked about the wording of the questions, stating that not finding an adverse effect either means that there is no adverse effect or that the testing technology is insufficient. The current results could mean either thing. Dr. Kieburtz said that the current state of knowledge is characterized more by uncertainty than certainty. Dr. Goldman agreed, saying that more studies should look at cumulative effects of mercury from diverse sources. Dr. Dourson said that the studies show evidence that mercury vapor is not causing problems. Dr. Goldman lamented the lack of information about immune defects.

Dr. O'Brien expressed reassurance about the safety of amalgams but concern of the cumulative effects of diverse sources of mercury. Dr. Dourson agreed, commenting that the exposure levels of those with amalgams comes very close to the limit of safe concentration. Dr. Goldman noted that there is no way of knowing that the uncertainty factor is sufficient, especially to protect fetuses. Dr. Kieburtz noted, pointing to questions 1 c and 1 d, that there is no direct evidence of impaired fetal outcome in people with amalgams, though there is for occupational exposure. He wanted to see neuropsychologic tests of the children.

The Committee discussed direct and indirect evidence, the paucity of direct evidence showing any adverse health effect of amalgams, the lack of information, the uncertainty about the actual exposure from amalgams, both the acute and, to a certain extent, in the chronic setting, how to best measure body burden, and apparently, a great deal of variability among individuals in the exposure they experience from amalgam use. Dr. O'Brien added the phenomenon of amalgams becoming electrolytic cells, dissolving the amalgam.

Mr. Alderson asked the Committee to elaborate on their concern for acute levels in relation to later clinical effects. Dr. Ascher said the concern was related to the potential cumulative effect of high level exposures that may manifest much later. Dr. Diamond was interested in immediate effects many presenters spoke of following an acute exposure. Dr. Dourson asked FDA to search for safe concentrations of mercury vapor after an acute or short-term exposure Dr. Dourson suggested looking at salivary mercury concentration. Dr. Honein suggested a closer look at occupational exposure to dental amalgams in relation to reproductive outcomes. Ms. Rosecrans said that is an OSHA matter.

Dr. Fleming noted the gap between medicine and dentistry that would prevent dentists from seeing any adverse events arising from amalgams. Dr. Rizzo agreed, noting that neurologists do not think about dentistry. Dr. Sacco cautioned on the value of registries.

2) 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?

The question went to a vote and was answered "no," 13 to 7. Those voting no cited knowledge gaps and the narrowness of the studies included. Those voting yes agreed that there were data gaps but felt that the data gaps were consistent with the current state of knowledge.

3) Given the amount and quality of information available for the draft FDA White Paper, are the conclusions reasonable?

The question went to a vote and was answered "no," 13 to 7. 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, since it was not the FDA's charge to create new data.

COMMITTEE SUMMATION

Before ending the meeting, Dr. Kieburtz polled the Committee for final comments to the FDA. Dr. Amar said that the Government must make informed consent happen. Dr. O'Brien commented that the literature shows that amalgam is generally safe, but care and attention must be used toward the risks. Dr. Dourson encouraged the FDA to meet with and learn from the public commentators, as well as to research the knowledge gaps, especially following up on the children studies. Dr. Goldstein wanted to see new data on exposure level estimations. Dr. Goldman recommended a broader, collaborative strategy be employed to gain broader knowledge. Dr. Zero identified a data gap: the effect of an acute exposure on adults already bearing a body burden. Dr. Ng felt that amalgam would

go away on its own but more needed to be known in the meantime. Dr. Hughes suggested a closer look at the literature and a look into what other countries are doing. Dr. Burton said FDA should take a broader look and readdress the issues. Dr. Kieburtz suggested looking into indicators that one will be a good or bad handler of mercury. Dr. Olson stressed the importance of informed consent, especially in women of child-bearing age, as well as studied in immunocompromised patients. Dr. Li emphasized that the hypersensitive population is larger than was suspected and hoped for identifiers of the risk. Dr. Taylor said that more focus should be placed on the constellation of experiences expressed during the public comment period. Dr. Sacco urged against a panic reaction before more study can be done. Dr. Rizzo emphasized informed consent and felt the White Paper should be broader and should explain why studies are excluded. Dr. Klaassen said that more research has to be done in general. Dr. Ascher suggested a broad look at mercury, to include environmental impact; comparing the exposure rates of amalgams and thimerosal, it is difficult to see why one is on the market and the other is not. Ms. Cowley suggested an awareness campaign and greater understanding of the potential adverse effects and emerging alternatives. Dr. Fleming advocated informed consent and restrictions on the use in high-risk populations, including pregnant women and young children. Dr. Kieburtz reiterated that the comments and votes were on the draft White Paper and did not mean an official recommendation for any change to the device. The discussion was for the FDA's benefit.

ADJOURNMENT

Dr. Alderson thanked the Committee, presenters, and public and noted that everything submitted is publicly available. Dr. Kieburtz thanked all of the participants and adjourned the meeting at 4:52 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 7, 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

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Karl Kieburtz, MD, MPH
Chairman

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