UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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DENTAL PRODUCTS PANEL

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December 15, 2010
8:00 a.m.

Holiday Inn
Gaithersburg, Maryland

PANEL MEMBERS:

MARJORIE K. JEFFCOAT, D.M.D.	Chair
KENNETH J. ANUSAVICE, Ph.D., D.M.D.	Voting Member
JOHN J. DMYTRYK, D.M.D., Ph.D.	Voting Member
AMID I. ISMAIL, B.D.S., Dr.P.H., M.B.A.	Voting Member
CLARK M. STANFORD, D.D.S., Ph.D.	Voting Member
JOEL M. WHITE, D.D.S., M.S.	Voting Member
MICHAEL ASCHNER, Ph.D.	Temporary Non-Voting Member
MICHAEL BATES, Ph.D.	Temporary Non-Voting Member
THOMAS M. BURBACHER, Ph.D.	Temporary Non-Voting Member
MICHAEL DOURSON, Ph.D.	Temporary Non-Voting Member
MICHAEL FLEMING, D.D.S.	Temporary Non-Voting Member
SUSAN GRIFFIN, Ph.D.	Temporary Non-Voting Member
JANINE E. JANOSKY, Ph.D.	Temporary Non-Voting Member
SURESH KOTAGAL, M.D.	Temporary Non-Voting Member
WILLIAM O'BRIEN, M.S., Ph.D.	Temporary Non-Voting Member
VAN P. THOMPSON, D.D.S., Ph.D.	Temporary Non-Voting Member
NORMAN TINANOFF, D.D.S.	Temporary Non-Voting Member
JUDITH ZELIKOFF, Ph.D.	Temporary Non-Voting Member

PANEL MEMBERS (Cont.):

MICHAEL D. BUI, D.D.S., M.P.H., J.D.	Industry Representative
JO-ELLEN DE LUCA	Patient Representative
KAREN R. RUE	Consumer Representative
OLGA I. CLAUDIO, Ph.D.	Designated Federal Officer
JAMES SWINK	Designated Federal Officer

FDA REPRESENTATIVES:

ANTHONY WATSON, B.S., M.S., M.B.A.
Director, Division of Anesthesiology, General Hospital Infection Control, and Dental Devices

PETER GOERING, Ph.D.
Center for Devices and Radiological Health

MICHAEL E. ADJODHA, M.ChE.
Engineer, Dental Devices Branch

OPEN PUBLIC HEARING SPEAKERS:

DORICE MADRONERO
PENTTI J. NUPPONEN, D.M.D., MAGD, CNC, FIAMOT
FREDRICK EICHMILLER, D.D.S.
SUZANNE BEAUDOIN, RDH
CLINTON ZIMMERMAN
JESSICA KERGER
VINCENT C. MAYHER, D.M.D.
STEPHEN MARKUS, D.M.D.
FREYA KOSS
JOHN KALL, D.M.D.
MARIE FLOWERS
ANDREA BROCKMAN, B.S.N., D.D.S.
SARAH MOORE-HINES
ANDREW READ-FULLER
SYLVIA DOVE
KATINA MINNEY
KAREN BURNS
DAVID KENNEDY, D.D.S.
KELLY GALLAGHER
ROBERT E. REEVES, J.D.
JAMES N. COOPER, D.D.S.
ALLEN ROBERSON
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M E E T I N G

(8:00 a.m.)

DR. JEFFCOAT: I would like to call this second day of the meeting of the Dental Products Panel to order.

I'm Dr. Marjorie Jeffcoat, chairperson of the Panel. I'm a professor at the University of Pennsylvania, and my -- and I am a periodontist and my expertise is in clinical studies.

At this meeting the Panel will discuss and make recommendations on specific scientific issues raised in petitions received by the FDA concerning the final rule of the classification of dental amalgam, which was published in the *Federal Register* on August 4, 2009.

Issues raised in the petitions include the adequacy of the risk assessment performed by the FDA in classifying dental amalgams in light of the new report on risk assessments issued by the National Academy of Sciences entitled "Science and Decisions Advancing Risk Assessment," and that is in the *National Academy Press* 2009.

Before we begin I would like to ask our distinguished Panel members and the FDA staff seated at the central table to introduce themselves. Please state your name, briefly your area of expertise, your position and affiliation. Can we start with Dr. Bui?

DR. BUI: Michael Bui from Bayer Pharmaceuticals. My expertise is clinical regulatory and I'm an Industry Rep.

DR. JEFFCOAT: Thank you.

MS. RUE: I'm Karen Rue from Lafayette, Louisiana. I am with Griswold Special Care and Life, Consumer Representative.

MS. DE LUCA: Jo-Ellen De Luca, Spartanburg, South Carolina. I am the Patient Representative.

DR. THOMPSON: I'm Van Thompson, chair of biomaterials and biomimetics at New York University, and I am here as a consultant to the Panel.

DR. ISMAIL: Amid Ismail from Temple University. I'm professor and dean of the school. My area of expertise is epidemiology, public health and disparity research.

DR. FLEMING: I'm Michael Fleming. My expertise is in the area of dental clinical sciences. I'm in private practice in Durham, North Carolina for over 30 years and I'm a consultant to the Panel.

DR. ASCHNER: My name is Michael Aschner, I'm a professor in the Department of Pediatrics at Vanderbilt University Medical Center, and my interest is in toxicity of metals, both developmental and -- that's it.

DR. ZELIKOFF: My name is Judith Zelikoff. I'm a professor at New York University School of Medicine in the Department of Environmental Medicine. I'm an immunotoxicologist. My interests are in inhaled pollutants with a special emphasis on metals.

DR. WHITE: My name is Joel White. I'm a professor at the

University of California San Francisco. I'm a practicing dentist who teaches and does research in dental materials.

DR. STANFORD: I'm Clark Stanford. I'm associate dean for research at the University of Iowa in Iowa City. I'm a prosthodontist and I do -- I have a research area that deals with developmental biology and stem cell differentiation on metal surfaces.

MR. SWINK: My name is James Swink. I'm a Designated Federal Officer at the Food & Drug Administration.

DR. CLAUDIO: Olga Claudio, Designated Federal Officer, Food & Drug Administration.

DR. DOURSON: Michael Dourson, board-certified toxicologist with Toxicology Excellence for Risk Assessment, a non-profit consultancy. Before that I did 15 years with U.S. EPA and in both cases I was doing environmental risk assessment, including development of reference -- and reference concentrations and research related to both.

DR. ANUSAVICE: Hi, I'm Ken Anusavice. I'm professor emeritus at the University of Florida, College of Dentistry, and I'm currently in the Department of Operative Dentistry. I was formerly associate dean for research for 13 years and retired -- semi-retired in April, and my principal areas of research are biomaterial science with specialty in prosthodontic materials and some research, NIH-funded studies of controlled release of therapeutic agents in resin sealants to prevent secondary carries.

DR. TINANOFF: My name is Norman Tinanoff. I'm professor and chair of the Department of Health Promotion and Policy, University of Maryland. My area is expertise is pediatric dentistry, clinical trials and preventive agents.

DR. BATES: I'm Michael Bates. I'm an epidemiologist and a professor of -- in the School of Public Health at the University of California Berkley.

DR. DMYTRYK: I'm John Dmytryk. I'm a periodontist at the University of Oklahoma. I have a Ph.D. in biology and I serve as associate dean for research.

DR. BURBACHER: I'm Tom Burbacher. I'm a professor at the University of Washington, School of Public Health, and my expertise in research has been in ethylmercury developmental toxicology.

DR. GRIFFIN: I'm Susan Griffin. I'm a toxicologist with the U.S. Environmental Protection Agency in Colorado, and my expertise is in exposure assessment studies for inorganics and the development of toxicity values for EPA.

DR. JANOSKY: Janine Janosky, Vice President, Austin BioInnovation Institute in Akron, Ohio; professor of biostatistics at the University of Akron, and professor of community health at NEOUCOM. I'm a biostatistician and a consultant to the Panel.

DR. KOTAGAL: Suresh Kotagal. I'm a pediatrician and pediatric

neurologist and professor in the Department of Neurology at Mayo Clinic in Rochester, Minnesota.

DR. O'BRIEN: I'm Bill O'Brien, professor emeritus of dental materials at the University of Michigan. I do research in dental materials and I'm a editor of a textbook called *Dental Materials and their Selection*.

MR. WATSON: I'm Anthony Watson, I'm the Director of the Division of Anesthesiology, General Hospital, Infection Control and Dental Devices, and I'm an engineer.

DR. JEFFCOAT: Thank you very much.

If everyone in the room has not already done so, please sign the attendance sheets outside the door that are on the tables by the door.

Now, Dr. Olga Claudio, our Designated Federal Officer for the Dental Products Panel, will make some introductory remarks.

DR. CLAUDIO: Good morning everyone. I will now read the Conflict of Interest Statement, FDA Conflict of Interest Disclosure Statement, Particular Matter of General Applicability, Dental Products Panel of the Medical Devices Advisory Committee.

The Food and Drug Administration is convening today's meeting of the Dental Products Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and consultants of the Panel are special Government employees or regular Federal employees from

other agencies that are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest law covered by, but not limited to, those found at 18 U.S.C. Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special Government employees who have financial conflict when it is determined that the Agency's need for a particular individual's service outweighs his or her potential financial conflict of interest. Under Section 712 of the Food, Drug & Cosmetic Act, Congress has authorized FDA to grant waivers to special Government employees and regular Government employees with potential financial conflicts when necessary to afford the Committee essential expertise.

Related to the discussion of today's meeting, members and consultants of this Panel who are special Government employees have been screened for potential conflict of interest of their own, as well as those imputed to them, including those of their spouses or minor children and, for the purposes of the 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants and

CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

Today's agenda involves a discussion of scientific issues raised in petitions received by the FDA concerning the final rule on the classification of dental amalgams, which published in the *Federal Register* on August 4, 2009. The issues raised in the petitions include the adequacy of the risk assessment performed by the FDA in classifying dental amalgams in light of a new report of risk assessment issued by the National Academy of Science entitled, "Science And Decisions, Advising Risk Assessment," NAP 2009. This is a particular matter of general applicability meeting then in which general matters related to dental amalgams will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waiver have been issued in accordance to -- with 18 U.S.C. Section 208 and Section 712 of the Food, Drug & Cosmetic Act. However, we would like to note for the record that a conflict of interest waiver was -- has been issued to Dr. Robert Yokel, who is a guest speaker with us today and will be making a -- made a presentation yesterday.

Dr. Yokel's waiver address his stock holding in a competing firm with a current value between $25,001 and $50,000. The waiver allows this individual to participate solely as a presenter at this meeting. FDA's reason for issuing the waiver as described in the waiver document, which is posted

on the FDA website at http://www.fda.gov/AdvisoryCommittees/default.htm. Copies of the waiver may also be obtained by submitting a written request to the Agency Freedom of Information Office, Room 630 of Park Lawn Bldg. A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

Michael Bui, D.D.S., M.P.H., J.D., is serving as the Industry Representative acting on behalf of all related industry and employed by Bayer Healthcare Pharmaceuticals, Inc.

We would like to remind members and consultants that if the discussion involve any other product or firm not already on the agenda for which an FDA participant has a personal or purely financial interest, the participant is to exclude themselves from such involvement and they're exclusion will be noted for the record. FDA encourages all participants to advise the Panel of any financial relationship that they may have with any firm at issue.

Ms. Joe Ellen De Luca has been appointed as a Temporary Non-Voting Member of the Dental Products Panel for the duration of the meeting on December 14 and 15, 2010. For the record, Ms. De Luca is a Patient Representative to the Gastrointestinal Drugs Advisory Committee in the Center for Drug Evaluation and Research. This special Government employee has undergone the customary conflict of interest review and has reviewed the material to be considered at this meeting. This appointment

was authorized by Jill Hartzler Warner, J.D., Acting Associate Commissioner for Special Medical Programs on December 7, 2010. Thank you.

Before I turn the meeting back over to Dr. Jeffcoat, I would like to make a few announcements. Transcript of today's meeting will be available from Free State Court Reporting, Inc. Telephone (410) 974-0947. Information and purchasing videos of today's meeting can be found on the table outside the main room.

I would like to remind everyone that members of the public and the press are not permitted in the Panel area, which is the area beyond the speaker's podium.

The press contact for today's meeting is Karen Riley. I request that reporters please wait to speak to the FDA officials until after the Panel meeting has concluded.

If you are presenting in the Open Public Hearing today and have not previously provided an electronic copy of your slide presentation to the FDA, please arrange to do so with Mr. James Clark at the registration desk.

Finally, please silence your cell phones and other electronic devices.

I want to make one more announcement, is that copies of the questions of the questions for the Panel consideration will be available shortly at the registration table. Thank you very much.

Dr. Jeffcoat.

DR. JEFFCOAT: Thank you.

We will now continue with the second session of the Open Public Hearing of this meeting. Public attendees are given an opportunity to address the Panel, to present data, information, or views that are relevant to the Panel meeting agenda.

Dr. Claudio will now read the Open Public Hearing Disclosure Process.

DR. CLAUDIO: At the beginning of your written oral statement please advise the committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. You will have 4 minutes for your remark. When you begin to speak the green light will appear. A yellow light will appear when you have 1 minute remaining. At the end of 4 minutes a red light will appear and your presentation should be completed. Since we have a number of speaker it is very important to adhere to the four minute limit. Each speaker -- as a speaker concludes their remark, Mr. James will guide the next speaker to the podium.

The Panel will be given an opportunity to ask questions of the public presenters at the conclusion of the Open Public Hearing. If recognized by the chair, please approach the podium to answer questions.

I would like to recommend all public observers at this meeting

that while this is meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

DR. JEFFCOAT: The first speaker this morning will be Ms. Dorice Madronero.

MS. MADRONERO: Yeah.

DR. CLAUDIO: And you can correct me --

MS. MADRONERO: No, that was a great job.

DR. JEFFCOAT: Okay. Please come forward to the microphone, which you've already done.

MS. MADRONERO: Yes, thank you.

DR. JEFFCOAT: And we ask that you speak clearly -- this is for everybody -- to allow the transcriptionist to provide an accurate transcription of the proceedings this morning. Thank you.

MS. MADRONERO: Thank you.

Good morning, distinguished Panel. Expectant parents -- oh, by the way I'm here as a taxpayer and a citizen, I don't have any financial interests here other than that.

Expectant parents are filled with hope for the future and dreams of what their children can be. Imagine those dreams being shattered what can easily be avoided. I can. That's what I ask this Panel to give a very careful look at how gaps in data and even preconceived beliefs about dental amalgam can profoundly affect people's lives.

Do gaps in data equate to proof of safety or viability of a fetus exposed to mercury? 2006, at the FDA hearing, Dr. Lynn Goldman: "But I come out of this very uneasy about what we don't know about both the exposure levels during dental procedures, what the transfer of that might be to the fetus, and what the impact of that might be on the developing brain, and everything we know about other forms of mercury, methylmercury, the times -- it seems to be a critical time, as during brain development in utero."

And so that is what is most important, things to know in terms of assessing safety, and we do not know it.

Dr. DeRouen: Amalgam fillings during pregnancy are linked to cleft pallet. Among mothers who have amalgam fillings the number of fillings they have correlates with mercury measured in cord blood and breast milk. Specifically, the fetal lip and pallet closed between weeks 5 and 10 of pregnancy, and new placement of fillings leads to a transient higher mercury concentration that peaks at about eight to nine-fold normal levels 1 to 2 weeks after the filling has been placed.

FDA's guidance for industry labels. The developing neurological systems in fetuses and young children may be more sensitive to the neurotoxic effects of mercury vapor are very limited. To note, clinical information is available regarding long-term health outcomes in pregnant women and their developing fetuses, children under the age of 6, including infants who are breastfed. Mercury vapor concentrations are highest

immediately after placement and removal of dental amalgam but decline thereafter.

As a young expectant mother I know that twice following dental work I miscarried. I know that at the time the dentist gave no warning about a mercury exposure. I know that at no point in my visits to the obstetrician was I warned about a mercury exposure, in the dental fillings or asked about my medical and dental history. I know that it in my visits to any physician or dentist I was never asked whether I'm allergic to mercury. Oh, I didn't drink coffee. I never smoked in my life and didn't even have a sip on New Year's Eve champagne.

FDA believes that in order to provide reasonable assurance of the safety of dental amalgam it is important that dentists are informed that the device contains mercury.

Should a pregnant woman be told that 50% of what is being installed in her teeth is mercury and that the ADA -- the FDA lacks data on safety of that exposure? Dr. Lynn Goldman, 2006: I was certainly taught that exposure to mercury from amalgam is minimal, that one shouldn't think about mercury toxicity from amalgam absent of proof.

The final ruling on dental amalgam is rife with assertions that dental amalgam is safe. In addition there is very limited to no clinical information available regarding --

DR. JEFFCOAT: You have 1 minute. Brief.

MS. MADRONERO: -- regarding long-term health outcomes in pregnant women and their developing fetus' and children under the age of 6, including infants who are breastfed.

Can you really say you don't know and then conclude safety? Are we going to perpetuate the myth that mercury, while dangerous and safe in mouth -- is safe in your mouth? Should the myth of safety overshadow public health? This myth of safety is like a mermaid; something that gets talked about but no one has ever actually seen one.

Mercury, the great masquerader, has duped us into false sense of safety, but mercury's transformative powers also delivers a message of harm. During the season of hope and light let us align that the reality that mercury is a poison and does not belong in teeth and surely not in a fetus.

And I have a question with regard --

DR. JEFFCOAT: Ten seconds.

MS. MADRONERO: Okay. Why is a voting Panel of dentists making a medical determination on the well-being of a fetus and child? Thank you.

DR. JEFFCOAT: Thank you. Appreciate it.

Next speaker is Pentti J. Nupponen, and please say that for the record because I'm sure I didn't say it properly.

DR. NUPPONEN: Oh, that was close. That was close. That is a name from a Finish orientation.

DR. JEFFCOAT: Okay.

DR. NUPPONEN: That's why it sounds a little bit different.

DR. JEFFCOAT: Thank you. And you have 4 minutes, sir.

DR. NUPPONEN: Thank you, ma'am. Thank you everybody. I'm Pentti Nupponen, with a 30-year dental career, but I'm a quack. I'm a quack. That's what all my neighboring dentists are calling us. So let's see --

Oh, before that, remember, we only do dentistry; we do not do medicine. Let's see what the quack has done with some of the patients.

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

Exposure to mercury from amalgam fillings, single amalgam filling during pregnancy results in autism. Here is a clear case of connecting dental mercury to autism. This Mennonite lady had nine children, five boys, four girls. When she was pregnant with her last child she had to go to a dentist. The dentist assured her that the filling is perfectly safe, the silver filling is safe, "ADA tells me so, so it is safe." And he placed one silver filling

into her tooth. Soon after that her blood pressure shot up to 180 to -95 and stayed that way from 2 to 3 years. And when the son was born he wasn't the same as the other eight. He was screaming all the time. He wouldn't look at her to the eyes. He had all the symptoms and signs of autistic child. In fact, he was diagnosed as an autistic child.

Remember, this family, none of them had any vaccinations. The only source for mercury for this little boy was from the amalgam filling put into the mother's tooth while she was pregnant with him.

So who is responsible? Is a dentist responsible? Is a dental establishment who absolute refuses to talk to dentist about the mercury amalgam toxicology? Are you, the Dental Board, responsible? Or is FDA responsible? The courts will decide.

Now, back to our profession. Dental mercury exposure is hurting and killing our professional members.

DR. JEFFCOAT: Sir, you have 1 minute.

DR. NUPPONEN: Thank you, ma'am.

Students of dentistry, hygiene and assisting students have career-long toxic exposure. Dentists have a higher than average suicide rate and the dental assistants have a higher than average miscarriage rate. It is not just an accident.

There's no -- absolutely no reason to use this pre-Civil War material anymore. Monday, this week, I checked, there was a 765 different

composite filling resign choices for dentists to use in place of amalgam filling; there's no need for this anymore.

DR. JEFFCOAT: Twenty seconds, sir.

DR. NUPPONEN: Thank you.

Clifford Dental Lab has done 40,000 tests, reactivity tests and not one was okay with amalgam filling. Please, you can make medical history today. Make your decision with your heart, not with your wallet.

DR. JEFFCOAT: Thank you for that very --

DR. NUPPONEN: I'll --

DR. JEFFCOAT: Thank you for your interesting presentation, sir. We appreciate it. It was very interesting.

And our next speaker is Suzanne Beaudoin.

MS. BEAUDOIN: Yes. Yes, ma'am, thank you.

I have a --

DR. JEFFCOAT: Thank you.

MS. BEAUDOIN: -- PowerPoint, though, it should be coming up.

DR. JEFFCOAT: They don't -- did you --

MS. BEAUDOIN: Can I -- I brought my --

DR. JEFFCOAT: Did you not give it in at the --

MS. BEAUDOIN: Yeah, I did.

DR. JEFFCOAT: Okay, let's go to the next speaker and see if you can -- if they can get it up for you, all right? If that's all right?

MS. BEAUDOIN: Yes.

DR. JEFFCOAT: Dr. Frederick Eichmiller.

We'll get back -- we'll come back to you, I just want you to be able to present your presentation if it's here.

DR. EICHMILLER: Good morning.

DR. JEFFCOAT: Thank you.

DR. EICHMILLER: My name's Dr. Fred Eichmiller, I am vice president and science officer for the Delta Dental of Wisconsin. I speak today on behalf of Delta Dental Plans Association, which is representing 39 affiliated companies that serve nearly one-third of the estimated 173,000 Americans with dental benefits.

The Delta Dental Plans Association fully supports the 2009 reclassification ruling on dental amalgam and the lengthy and thorough process through which that ruling was made. That process, we think, properly weighed the potential risks against the well-documented benefits of dental amalgam. And in our October 18th written response to the public comments, we supported the benefit of amalgam by citing a 2007 publication, "Economic Impact of Regulating the Use of Amalgam Restorations," which was published the September and October issue of *Public Health Reports*.

This article clearly spelled out the huge economic costs of restricting or eliminating the use of amalgam, and further emphasized the

current economic benefits of amalgam.

The report offered by Dr. Richardson to the International Academy of Medicine and Toxicology really provided no new evidence of harm by dental amalgam. This report was a compilation of estimates and assumptions that hasn't really been peered reviewed at this point or subject to any type of evaluation expected for evidence brought before this Agency. The estimates made of amalgam burden don't take into account common knowledge of clinical use and extrapolate results from very small cohorts to the entire U.S. population.

One example I can provide is an error in the estimate of amalgam surfaces. For the youngest aged cohort of 2 to 5, has a mean of 14.6 surfaces with a maximum 72. This was derived from a total of 94 children examined a 2001 to 2004 NHANES surveys, which doesn't identify either filling types or materials.

To compare, I pull claims data from the same time period using an age cohort of 0 to 6 so I could get all episodes of care. And of that cohort it included just over 1.6 million children, and of which about 267,000 or 16.7% received one or more amalgam fillings over that period. This is the lowest percentage of any age cohort within the total population of 26 million included in this analysis.

Breaking these fillings down by tooth showed that 97.3 of amalgam restorations were placed on primary molar teeth, with only 1.8% on

anterior teeth, being mostly primary cuspids. What this indicates is that amalgam is limited almost exclusively to the 8 primary molar teeth making the 14.6 and the 72 amalgam surface numbers both highly implausible and physically impossible.

The 676,000 amalgam restorations that were placed averaged 2.53 restorations per child over this period, and of those, 39.3% were single-surface, 54.3% were two surface, only 5.7% were three surface, and less than .7% were four surface. Stainless steel crowns are generally recommended for primary teeth requiring three or more surfaces and this data supported that practice. Using this distribution of fillings, the average child during this period acquired 4.24 surfaces of amalgam.

Similar discrepancies were obvious in other age cohorts. An example I can show is the use of the maximum number of potential surface for an adult of 100, where our data shows that it is almost -- amalgam is almost exclusively used on the 16 posterior teeth so it would be very difficult to achieve those. And it was quite obvious from the NHANES data that those were patients that received crown restorations.

Amalgam remains a frequently chose option for our insured clients and a vitally important option for the underserved and we firmly believe that the FDA has ruled in the past by considering a reasonable balance of risk versus benefit and we hope that they will continue to do so in order to preserve this critically important right and ability of consumers to

choose. Thank you.

DR. JEFFCOAT: Thank you very much.

Do we have that presentation? Okay, Ms. Beaudoin, would you -- thank you for letting us get your presentation up.

MS. BEAUDOIN: Well, thank you for letting me be here today.

I have a dream that one day all dental fillings placed will be mercury free. How do you advance? Okay.

The mercury mischief: As Obama warns of hazards, the FDA approves mercury dental fillings. I just want to read a little bit. The risks -- the plan stated as a fundamental goal, reduce risk of mercury pollution. More than 5 million women of child-bearing age have had high levels of toxic mercury in their blood and approximately 630,000 newborns are born at risk every year.

The EPA estimates that every year more than 1 in 6 children could be at risk for developmental disorders because of mercury exposure in the mother's womb. The truth is the FDA has never tested mercury fillings for their safety.

The United States of America stands for freedom, liberty, justice and the pursuit of happiness. Mercury used for dental fillings is toxic, in and out of the body.

I'm a dedicated -- I'm bright, dedicated and licensed dental hygienist. I honor the ADA standards for clinical dental hygiene practice of

2008. I'm here today to help bring an end to the usage of toxic mercury in dental fillings for the people in the United States by sharing my mercury poisoning journey and how it has impacted my life.

My exposure to toxic mercury from ages 7 to 16, I received 16 amalgamated high silver -- high copper-mercury-silver fillings. From MC through adulthood, especially being a provider of dental healthcare, I received immunizations laced with mercury as a preservative.

I trusted the ADA and the FDA. I was told as a dental assistant that I was working safe when I brought out excess mercury using only a cheesecloth. Then as a dental hygienist I was assured that hand scaling and ultrasonic usage around amalgams was considered safe. I wasn't informed about mercury's fumes or the buildup of mercury's toxicity in my blood, organs and brain tissues, or that it passed into my baby's placenta. My concerns about mercury toxicity were ignored or thought disloyal to the ADA.

Traditional dental offices are toxic places. I now seek a safe dental practice to practice in.

My endangered health, athletic stamina, mental focus decline: severe mononucleosis grade 6 and 10, extreme fatigue limiting income, gluten intolerance, gallbladder/liver issues, dizziness, vertigo resulting in falls, hand tremors and tingling sensations, chronic tinnitus and hearing loss. I do wear hearing aids. Adrenal and thyroid and pancreas insufficiencies.

My systemic mercury poisoning journey: I ended my toxic

exposure to mercury poisoning. I resigned from traditional dental hygiene practice. I refused mercury containing vaccinations. I follow holistic health practices for detox. I am forced to have a slower-paced lifestyle with an income loss for quite a while now. Nutritional healing is gluten-free, organic, et cetera. I do -- I'm a licensed or a certified Wu Ming Qigong instructor for meridian balancing to try to help myself there and I study the oral systemic link because early assessments do save lives.

Truth: Mercury in any form --

DR. JEFFCOAT: You have 1 minute, ma'am.

MS. BEAUDOIN: -- is toxic. For the health of our families outlaw all mercury factories and all mercury fillings. Let us together stop this needless suffering and create dental environments that foster safe therapies and rebuild trust.

And I would like to ask a question. I know it's rhetorical. I have a professional ethical dilemma. I have pledged to inform my patients and to do no harm to them. As a licensed dental hygienist who is aiming to fully recover from mercury poisoning, how am I to answer my patients' questions posed to me in regards to the absolute and soundness of mercury fillings? Thank you very much.

DR. JEFFCOAT: Thank you.

Our next speaker is Holly Harvin. Holly? No? Not here. Okay.

James -- Dr. James Cooper.

Is Dr. Zimmerman here? Clinton Zimmerman? Clinton Zimmerman, okay. Thank you.

MR. ZIMMERMAN: Also in the conflict of interest -- interest of conflict of interest you should know that my dad currently works for the FDA, is a review chemist at CDER.

My name is Clinton Zimmerman and I believe I suffered from amalgam poisoning. I live in Gaithersburg. I'm an electrical engineer. I would like to briefly tell you my story and then make some observations.

After having a filling placed at 12, I began to have symptoms associated with mercury starting at about 16. Though not very noticeable with progressed -- becoming really pronounced around 21, about 9 years after the placement of the filling, up to 27, when the filling was removed, I experienced the following symptoms: frequent urination, burning in chest, fatigue and inability to complete assignments on time, memory loss, anger issues which previously had not existed, handshaking when soldering circuits, thyroid problems, strange jaw infections, loss of intelligence, strange stains on my teeth and so on.

When I had my fillings removed at 27, instead of getting worse I started to get better and improved tremendously after treatment with ALA following the Cutler Protocol, but with less dosing cycles.

When I had my fillings removed there was a tremendous decay above the filling according to the dentist who removed it and he said,

"Insurance will pay for removal of that filling." He was a traditional dentist, by the way, though he did not initially believe fillings could be harmful.

I believe that the filling may have been placed poorly, but the filling, which was in close proximity to another filling, may have undergone galvanic reaction and/or that there was methylation on the surface of the filling.

That brings me to the following points. What's standards are used in any dental office? What tests are done by doctors to assess toxicity in non-ideal conditions? In fact, under ideal conditions the ADA analysis is a house of cards based on invalid assumptions.

For example, virtually all ADA citations assume that urine testing is accurate, but this is not proven. I am -- a study I am holding here, a "Urine mercury and micromecurialism bimodal distribution diagnostic implications," published by Bolton of *Environmental Contamination and Technology* says, "Low urine Hg alone does not rule out micromecurialism at first, but in fact is diagnostic for micromecurialism due to a phenomena called retention toxicity." That means there's two peaks. People that are mercury poisoned have -- excrete less mercury in the urine, not more. That's published since 1999.

You do not address methylation at the surface of the filling at all or the production of phil groups at the surface. Where are the studies on this? This is the single largest possible component to toxicity and here --

these hearings, discussion after discussion it's simply ignored by the ADA and the FDA. I mean, in the mouth, on top of the filling, not in the gut. You've not addressed the placement of fillings which are mixed poorly, put into galvanic contact with other metals. And so -- or that undergo crevice corrosion phenomena that take years to develop, put in by dentist's sloppy techniques. These are real conditions, and in a children's study, dentists that know they're placing fillings in, are putting them in under ideal conditions.

Another thought, have you considered the possibility that some fillings may lose mercury rapidly, say, in a galvanic reaction or poorly made? The amount of time --

DR. JEFFCOAT: You have 40 seconds, sir.

MR. ZIMMERMAN: The amount time to measure such release is inversely proportional to the amount of release. It would, in other words, be a spike, but you say we assume that it's a constant dose.

Finally, I think it is easy to forget the big picture. Using urinalysis is not the simplest measurement technique. Measuring the amount of mercury left by weight is. Studies show, by weight, that fillings loose large amounts of mercury, up to 50%. As an engineer, I can tell you that the mercury has gone somewhere for if half of what goes into a black box comes out, half remains in the black box.

DR. JEFFCOAT: You need to wrap it up in 10 seconds, please.

MR. ZIMMERMAN: Thank you very much.

DR. JEFFCOAT: Thank you. Thank you, Mr. Zimmerman.

DR. JEFFCOAT: Has Holly Harvin arrived? Okay.

Dr. Cooper; has Dr. Cooper arrived?

Yeah, Jessica Kerger?

MS. KERGER: I had a handout. Did everybody receive that? It's got an Athena diagnostics test result on the front?

DR. JEFFCOAT: Um-hum.

MS. KERGER: About nine pages? Okay.

I am Jessica Kerger. I got to tell you I am so blessed and happy to be able to stand here and talk to you today. It's just a wonderful thing for me and I so appreciate your willingness and interest in hearing us all talk.

My husband is my financial source. I certainly have no conflict. This is my Christmas present right here, this trip. I testified in 2006 that my own health took a stunning nose-dive into frank disability, social security disability after I had root canal performed through an amalgam filling.

Now, I should mention that my situation, my health situation was already compromised. I already had diagnoses such as chronic fatigue syndrome, neurocardiogenic syncope, chronic Esptein-Barr, chronic urinary tract infections and sleep disorders, so I was already in a bad spot but then I had this procedure done through that amalgam filling.

Within days of that I lost my ability -- I'm a trial lawyer -- I lost my ability to even put together a simple "To Do List." My daughter was

graduating from kindergarten, I couldn't put like four tasks in a row. I would start driving and not know where I was or where I was trying to go. At one point I even left my 7-month infant on a changing table, went to go get him a diaper and didn't come back. When I realized, I don't know how many minutes later that he was missing -- I mean, that he was crying, my response was anger. I was home alone with him. So I really struggled.

But the good news is here I have no more tremor, not in my mouth, my eyelid, anywhere. No more stocking-glove paresthesia of the hands and the feet, no chest pain, no migraine, no double-vision, no eyelid droop, no tinnitus, no sour metallic taste. I've recovered part of my IQ. I'm off social security disability. I'm back to practicing law. I'm helping my husband finally help raise our three spectrum children. They're all highly functioning, thank God, but it's still quite a bit. I still have memory and executive function problems; I still lose things, just not children.

What I want to help you with today is your question 2(d), which is: "Are there other specific age-related physiological, genetic or pharmacokinetics differences of mercury vapor exposure that should be considered in your risk assessment?" I think it's important to note that our chairwoman wrote an interesting quote while she was the editor of the *Journal of the American Dental Association* and she was writing about junk science but this is what she said about case reports: "Case reports, which may deal with as few as one interesting patient, are a cornerstone of clinical

science. They are no less scientific for their descriptive, as opposed to statistical character. History is full of instances in which alert clinicians have pointed the way through breakthroughs by sharing isolation observations with their colleagues. Case reports become junk" --

DR. JEFFCOAT: You have 1 minute. I didn't mean to interrupt you during my excellent quote, but --

MS. KERGER: Yeah, your own quote.

Anyway, you were saying that they can be valuable. I would like to walk you through as quickly as I can my own test results. I am ApoE 3 and 4, which means I'm at much greater risk for Alzheimer's. This test reports that I actually had, to a statistical confidence of greater than 97%, Alzheimer's at that time.

The next sheet is the genetic test for GSTM1, which is mentioned in your report on allergy and hypersensitivity. Also I have superoxide dismutase issues. Below that are my reduced glutathione and superoxide dismutase, which are factors which toxicologists have said that are related to mercury toxicity.

The following is my --

DR. JEFFCOAT: I need to ask you to wrap it up in 10 seconds.

MS. KERGER: All right, I'm sorry.

What I have to say is the statement that amalgam is safe and effective is complete baloney. It was not safe for me. Many people might be

able to tolerate it, but the only way to make mercury fillings safe is to effectively end their use. Thank you.

DR. JEFFCOAT: Thank you.

Our next speaker is Dr. Vincent Mayher and there are at the --

DR. MAYHER: Thank you.

DR. JEFFCOAT: Thank you.

DR. MAYHER: Hi. I'm Dr. Vincent Mayher, past president of the Academy of General Dentistry, an organization of over 35,000 dentists, the majority of whom are engaged in individual private practices.

We are the professionals who are out there in your communities, treating patients day in and day out. And because we establish long-term relationships with our patients nobody cares more about their health and welfare than we do.

I'll begin by dispelling a few misconceptions. First, the vast majority of dentists in private practice, myself included, are placing tooth-colored composites as their primary restorative material of choice. Many do place amalgams under certain circumstances.

Second, the overwhelming majority of dentists in private practice limit treatment on pregnant women to emergency or preventive services only. So for the most part we're not placing amalgam or composites in these individuals. And in my office I do not do any restorative work on a pregnant woman if it can wait until the end of the pregnancy.

And third, the vast majority of dentists in private practice place tooth-colored composites and/or glass ionomers in children's teeth; stainless steel crowns if it's a large restoration.

So these exaggerated accounts of dentists forcing amalgam into the mouths of pregnant women and children are inflammatory, breed mistrust and have no basis in fact. At least not in the private practice setting.

So when do dentists place amalgams? Let me give you an example. I recently had a patient return to my office after a prolonged absence. John was a man in his mid-60s, had been a patient of mine for a while. And why I asked him why he had been away he said he had lost his job and his wife was suffering inoperable cancer. Unfortunately, because of this absence he had two molars which were badly broken down well below the gum line and needed two full crowns.

When I mentioned this to him he replied that he had neither the time nor the money given his wife's situation to have this kind of dentistry done. Composites for me were not a viable option because I could not possibly maintain adequate moisture control to place these restorations this far below the gum line. However, two pinned retained amalgams could give John years of service until hopefully things got better for him.

I explained this alternative to him and I mentioned the fact that this material contained mercury, a known toxin, and he responded similar to the way most patients of his age do when presented with this information, he

said, and I quote, "Well, Doc, I've had a mouth of these things for many years and I've never had a problem with them." In the end I was able to restore full form and function using two amalgams in one visit at a fraction of the cost of two crowns. John was ecstatic and couldn't thank me enough.

Had I informed him that his choices were limited to two crowns or two extractions because big government removed amalgam as a viable option, he would have been pretty upset and I wouldn't blame him.

Understand, no patient should have any restoration placed in their mouth without their or their parent's full informed consent. Any decision to place any material in any patient's mouth must be made at the local level by an educated, well-informed patient after prudent and open discussion with their treating dentist.

I urge --

DR. JEFFCOAT: Doctor, you have 1 minute.

DR. MAYHER: Thank you.

I urge this Panel not to interfere with this relationship. Do not posture yourself between a patient and their treating dentist. Do not deprive our patients of one of their most basic rights, the right to make their own healthcare decisions. Thank you.

I have written material for you, as well.

DR. JEFFCOAT: Thank you very much.

Our next speaker is, I believe, Dr. Stephen Markus.

DR. MARKUS: Thank you for inviting me to speak, Dr. Jeffcoat and Panel. My name is Stephen Markus and I've been a general dentist in Philadelphia suburbs for 35 years since graduating from the University of Pennsylvania.

There are five paragraphs in the handout that come below that that I would like you to read because the 4 minutes doesn't give me enough time to present that.

Let me explain why we're here. Collectively we are here because around 1830 MDs in this country advocated against the use of mercury in anyone's head because of the newly imported technique of the use of dental amalgam.

The blacksmiths and barbers who also treated oral pain therefore formed a guild whose support of mercury could today be compared with that of the ADA. The ADA has in its Code of Ethics the fact that it is unethical to speak out against the use of mercury fillings. Perhaps that is why so many dentists don't even bothering thinking about the consequences of their continued use of mercury.

Personally, I'm here because my eyes were opened and my head came out of the sand when I read about the Vimy study performed in Canada over 20 years ago. Using a radioisotope of mercury in amalgams placed in sheep, Vimy sought to prove that mercury became inert. To his surprise he found that it distributed to all organ systems, but crossed the

blood/brain barrier much more than it distributed to the body. It crossed to the placenta to an even greater degree. The guild disputed those results claiming that sheep were different than humans. Vimy's results were then repeated in primates.

You, the Panel, are here because despite the last Panel's rejection of its own White Paper in 2006, and the admission by the FDA's author of said White Paper, that the reason all the information presented to that Panel was so one-sided and pro-amalgam was that "He was only following orders."

The FDA is under the influence of sinister forces that are trying to undermined health. Whose? I know both as a citizen and a dentist the decision last year by the FDA not to modify protocols used, not just for the placement of mercury amalgam but also to advocate for safe removal process, smacks of corruption.

The FDA asked me after the last time I spoke here what I thought about a ban against the placement of mercury fillings in the heads of children under 6 years old and in pregnant women? I told them it was a start but it did not go far enough. All the teeth in the head of a child at age 6 have begun to fall out, so what the proposed regulation did was permit the placement of mercury fillings into teeth that were going to remain in the body forever.

They wanted to prevent its placement in pregnant women. I

told them that the regulation should have begun at first menstruation, ended after menopause and was also sexually discriminatory. So what the FDA did was nothing. The status quo.

I have seen enough patient's conditions of depression, memory fog, Ménière's disease, fatigue and more eliminated after the proper protocols are followed to remove mercury. I have seen others where the dentist decided to a patient's request for mercury removal and their conditions worsened because proper protocols were not followed.

The FDA had an opportunity to correct a 180-year old wrong last year and the powers that be succumbed to a 180-year old sinister plot to poison Americans whose health is being compromised by a substance that 180 years ago was known by medicine to --

DR. JEFFCOAT: Forty-seconds.

DR. MARKUS: -- cause neurotoxicity.

It's time for the FDA to right a 180-year old wrong. Not only must this substance be banned but the public and MDs need to be educated about the symptoms and correct removal protocols which must be followed. Only mercury-safe dentists should be doing this removal.

DR. JEFFCOAT: Twenty seconds.

DR. MARKUS: How can I have any trust in government and any faith in the FDA when important decisions requiring simple protocol changes are not advocated by a government organization that is supposed to have the

best interests of its citizens and not sinister lobbies at the forefront of their resolutions?

DR. JEFFCOAT: Thank you very much.

Our next speaker will be Freya Koss. Koss.

MS. KOSS: Koss.

DR. JEFFCOAT: Koss. Got it right the first time. Sorry.

MS. KOSS: Okay.

DR. JEFFCOAT: Thank you, Dr. Markus.

MS. KOSS: Thank you.

My name is Freya Koss. I have been actively fighting this issue and testifying locally, internationally and nationally since 1998.

Thirteen years ago my life changed forever when I was suddenly struck with blinding double-vision and diagnosed with multiple sclerosis and lupus. Within weeks the symptoms exacerbated. Within the onset of drooping eyelids, loss of equilibrium, swollen mandibular glands and indescribable head pain which felt as though rubber bands had been tightly bound around my head; that's what I looked like. I think you should all turn around and take a look at that photograph. Three and a half years I walked around like that.

Based upon these clinical symptoms, together with abnormal blood results, including an extremely high autoimmune titer of 10,000, an elevated rheumatoid factor and liver enzymes, together with positive

antibodies to the acetylcholine receptor I was diagnosed with myasthenia gravis, an autoimmune disease causing a breakdown of the communication between the nerves and the muscles.

When questioning five neuro-ophthalmologists at teaching hospitals in Philadelphia what the causes of these diseases might be I was emphatically told that there is no known cause, no known cure and was literally told that I would be sick for the rest of my life; offering only steroids to fix my eyes and Mestinon to suppress the symptoms.

Rejecting what seemed to be a deadly prognosis, I initiated my own research and within 5 days discovered that the symptoms were the result of having been acutely poisoned by mercury during a drilling out and removal of an old amalgam filling only 7 days before I was afflicted with the neurological symptoms.

Little did I know at the time that so-called silver fillings were actually 50% mercury, a known neurotoxin and that there was a plethora of scientific evidence related to the toxicity of mercury from dental amalgams and a variety of autoimmune and neurological diseases, such as MS, lupus and myasthenia gravis.

One such government report was the 1991 evaluation of risks associated with mercury vapor from dental amalgam prepared by the subcommittee on risk assessment, the committee to coordinate environmental health and related programs which concluded that mercury in

the form of vapor is consistently released from dental amalgam and is absorbed rapidly into the bloodstream and distributed to all major organs and tissues. And mercury in blood can cross the blood/brain barrier where it can be retained in the brain. And that the mercury released from amalgam fillings in inhaled, ingested and found in saliva.

DR. JEFFCOAT: You have one moment, thank you.

MS. KOSS: Other studies reported that heavy metal, such as mercury from dental amalgam, can impair function of the skeletal muscle, acetylcholine and calcium channels to the motor nerve terminals compromising neuromuscular transmission. This is seen in myasthenia gravis.

I also learned from the research of Swedish neurologist Patrick Stortebecker that route for transport from the upper tooth to the brain amounts to less than 10 centimeters and that neurotoxins from the oral cavity can cause neurological symptoms such as double-vision and drooping eyelids as seen in myasthenia.

I also learned that I have a genetic predisposition not to be able to excrete mercury sufficiently.

DR. JEFFCOAT: Fifteen seconds, ma'am.

MS. KOSS: I have three sentences, may I please finish them?

I also learned that I have a genetic predisposition not be able to excrete mercury sufficiently, as indicated in an ApoE blood test. I am a 3-4, often seen in Alzheimer's disease. Based on --

DR. JEFFCOAT: Thank you . Thank you very much for your presentation. Appreciate it. We appreciate it and need everybody else to have the equal opportunity to speak.

John Kall.

DR. KALL: That's correct.

My name is Dr. Jack Kall. I serve as the chairman of the board of directors of the International Academy of Oral Medicine and Toxicology. For 33 years I've practiced general dentistry in Louisville, Kentucky.

In 1983, when I learned that mercury escaped from amalgam fillings I stopped placing them. Throughout the 1980s and into the '90s more research and analysis was published about the release of mercury from amalgam fillings, its distribution in the body and its path of physiology.

I'm very disturbed that the scientists who published the research in well-respected peer reviewed journals were not invited to participate in the most recent 2006 FDA hearings in dental amalgam. Ignoring the research on this issue is reprehensible.

Finally, at this hearing a few of them have been heard, not because the FDA invited them but because of the generosity of Petitioners Jim Love and Jim Turner giving up some of their allotted time.

Many patients have requested that I remove their mercury fillings so that they can eliminate an unnecessary and dangerous exposure to a known toxin. Some of these patients were having various symptoms

documented in the medical literature as being associated with mercury poisoning. Many of these patients experienced reduction and/or cessation of their symptoms.

In 1991, the World Health Organization published the following document, "Environmental Health Criteria, Volume 118, Inorganic Mercury." In it the consensus of their experts stated that the greatest non-occupational human exposure to mercury is from dental amalgam fillings in the range of 3 to 17 micrograms per day.

Mercury has been removed from paint, contact lens solution, topical disinfectants, nasal sprays and some vaccines. It should no longer be available for use in mercury fillings -- in dental fillings.

I'm continuously dismayed to hear my colleagues make the speechless argument that amalgams should not be banned because the alternative material composite is much too difficult place in areas of the mouth that are difficult to keep dry. Mechanical properties of dental materials are certainly an important factor to consider in treating our patients but it shouldn't be the most important factor.

I have used composite material exclusively in my practice for 27 years and personally know many other dentists who have done the same. We have learned techniques that have enabled us to overcome any difficulties in placing it in teeth. The toxicity of the material, in this case mercury, should preclude its use in a dental filling material.

In the interest of safe, ethical and professional care for dental patients in this county I expect that the FDA will fulfill their obligation to protect the public from the unfettered use of a grand-fathered material masquerading as what the American Dental Association claims is a safe and stable material.

How can anyone believe or trust the people who make the --

DR. JEFFCOAT: One minute, sir.

DR. KALL: -- incorrect analogy of a sodium and chloride -- chlorine bond and salt compared to the mercury bond of the other metals in an amalgam? Where is that high school chemistry book from yesterday? How could anyone believe or trust the people who make a ridiculous claim that it takes 500 amalgam fillings to see subtle symptoms? How can anyone believe or trust that the American Dental Association really has the public's best interest at heart when it's stated in a legal brief in 1995, "The ADA owes no legal duty of care to protect the public from allegedly dangerous products used by dentists. The ADA did not manufacture, design, supply or install the mercury-containing amalgams."

DR. JEFFCOAT: Twenty-seconds.

DR. KALL: "The ADA does not control those who do. The ADA's only alleged involvement in the product was to provide information regarding its use. Dissemination of information relating to the practice of dentistry does not create a duty of care to protect the public from potential injury."

Thank you.

DR. JEFFCOAT: Thank you.

Our next speaker is Linda Brocato? Brocato?

Is she here? She's not here. Okay. She is here? Excuse me, do we have -- no. Okay. We have to not have confusion, so are you reading for her and can you tell us your name, please?

MS. FLOWERS: I'm Marie Flowers. Linda Brocato is in a wheelchair today because of mercury induced multiple sclerosis. She wants you to know about a brochure that the American Dental Association put out and it was entitled, "Protect yourself and your staff from one of the hazards of your profession with the ADA mercury testing service".

The brochure states: The ADA wants you to stay healthy. Exposure to mercury is a potential hazard for anyone in the dental profession who handles mercury or mercury containing compounds. The potential symptoms of mercury exposure are scarcely recognizable in the beginning. Growing irritability, mood swings and appetite loss are not necessarily alarming at first. Neither is insomnia. But later tremors or numbness in the fingers can develop from prolonged exposures. Waiting for these symptoms to appear is far too late.

The next paragraph states: Complacency is dangerous.

Now, this was from a brochure in 1985. Now, it -- they say that the fillings are okay. The website for the ADA says: Dental amalgam is

considered a safe, affordable, endurable material that has been used to restore teeth for more than 100 million Americans.

But if you get on the IAOMT website and you see the smoking teeth poison gas video, you will see mercury vapor is constantly escaping from a dental amalgam filling, 24-hours a day, 7 days a week in the blood stream of a human body.

So if mercury-caused health hazards to dentists and the dental professions who handle the mercury or the mercury-containing compounds, what do they do to the human body that have the dental amalgams implanted in their teeth with escaping mercury vapors?

The 1985 brochure clearly states that the ADA knew that mercury was hazardous and resulted in health effects. The brochure was discontinued in 1988.

So Linda is saying that this is fraud. To constitute fraud the misrepresentation or omission must be made knowingly and intentionally, not as a result of mistake or accident or in negligent disregard of its truth or falsity. Also the plaintiff must prove that the defendant intended for the plaintiff to rely upon the misrepresentation and/or omission, that the plaintiff did not in fact reply upon the misrepresentation and/or omission, and that the plaintiff suffered injury or damage as a result of the fraud. Damages may include punitive damages as punished by a public example due to the malicious nature of the fraud. And yet ADA representatives yesterday get up

and say nobody is poisoned with this, when a dental assistant sits here with half of her brain paralyzed with neuropathy.

So the ADA's 1985 position that mercury is hazardous but superseded by the FDA's July 28, 2009 position that amalgam is safe for everyone.

The FDA is supposed to protect the health and well-being of the public, not harm them. This is a crime against humanity and Linda. You can see her in a wheelchair today because of this crime.

DR. JEFFCOAT: Thank you.

Our next speaker is Dr. Andrea Brockman.

DR. BROCKMAN: My name is Dr. Andrea Brockman. I am president of OraMedica International. I am a wellness consultant and educator of the dental connections to overall health. And I am very pleased to see this Panel, which reflects voting members of dentist, with also other advanced degrees, showing that you have an expertise and giving another perspective.

I also am a dentist and I have my bachelor of science degree in nursing, which also gives me a different perspective. I worked as a coronary care nurse and was taught at Temple Dental School, one of the first baccalaureate programs where I had my pharmacology, microbiology and physiology taught by medical school professors. My physiology professor gave me my recommendation to dental school and later became the dean of

Temple Dental School, Dr. Tanzin (ph.).

As a nurse we were taught to read labels on the drugs. We were taught to do extensive health histories and to recognize the side effects of drug interactions, changes in vital signs, behavior, look at laboratory test results that have changed. We measured things.

What we are talking about here is a medical consequence to a dental intervention. And this brings a problem because dentists are not permitted to practice medicine; we are not permitted to diagnose and treat health conditions, and there are not dentists around who are able to make that determination if a person is mercury toxic.

Combine that with the fact that physicians are really having an inadequate education in dentistry and that they know very little about what goes on in the mouth. When you open your mouth they look straight back to the throat and tend to overlook what is going on in the dentition. Also, they're really not taught very much about metal toxicity and mercury toxicity. We have a problem that there are no tests that accurately diagnose mercury toxicity.

We talked about how urine tests are inadequate because some people do not excrete. We talked about how blood tests are inadequate because the mercury with a zero valance goes directly into the cells and gets locked in and ionized; that does get locked in. So the fact that we have no reliable testing and the fact that dentists are not able to treat and diagnose

for it and the physicians are not able to actually diagnose and treat and do testing creates a void. There is a gap.

How can the patients know if they have symptoms and how can they know if they are mercury toxic, but they should be told --

DR. JEFFCOAT: You have 1 minute. Briefly.

DR. BROCKMAN: -- they should be told that there is mercury in their fillings. And the ADA has a responsibility to help educate through their website the dentists, the physicians and the consumers. Thank you.

DR. JEFFCOAT: Thank you so much.

Our next speaker is Sarah Moore-Hines.

MS: MOORE-HINES: Testing. It works, right?

DR. JEFFCOAT: It works.

MS. MOORE-HINES: The body is the temple of the soul. Or it should be.

A graduate of Swarthmore College, I received my masters in mental health from Hahnemann Hospital Graduate School in Philadelphia. I've been a professional counselor for over 30 years and I'm a nationally certified counselor. I served on two professional standards mental boards in Pennsylvania.

Fourteen years ago, as many, I was healthy, happy and physically active but then in 1996 after dental amalgam restoration work I began to experience again what many have: exhaustive fatigue and eventually couldn't

walk around the block. I ended up working part-time and blood tests indicated I was fine, so my doctors were at a loss. After 4 years I was diagnosed with mercury toxicity due to amalgam exposure. Please see the medical documents in front of you, my doctor's letter.

I discovered that mercury had damaged my immune system, thyroid and adrenals and I experienced increasing problems of memory, concentration, anxiety and depression. I read relevant scientific studies, such as the NHANES 3, in which thousands of people's health was monitored and concluded that there were significant correlations between amalgams and several chronic conditions, including mental health disorders.

Dr. Dietrich Klinghardt's work found that the mercury accumulates in and affects the limbic system, which you know is the primary -- one of the primary centers of emotions in the brain. Dr. B. Windham cites 26 studies that indicate mercury can cause depression and mood disorders by lowering levels of neurotransmitters.

Ten years ago I had my fillings safely removed and slowly began to recover on a medical treatment protocol that was pretty in-depth. I continue to do that, by the way, and my doctor and I agree that I fought, quote, "to get my life back."

Patients who come into my counseling practice who are not -- who do not respond well to therapy or to medications cause deep concern and compassion. Very often they are psychologically suffering, as well as physically,

from amalgam illness. When they are, they often have no clue as to why they're sick, as was in my case. But doctors may not suspect heavy metal toxicity. And the authorities, including the FDA, are not acknowledging the mercury content. So clients often feel confused, hopeless, despairing, fearful, even suicidal. Dentists, sadly, themselves have the highest suicide rate of any professional. It's shocking. So other layers of hardship, then, because of the denial of the system, along with internal amalgam assault to the body and mind, creates a profound need for disclosure of the potential harms of mercury. This is a significant issue of consumer protection, public safety and basic justice.

So what are our options? Ban amalgam, the most obvious one. Second to that, recall amalgam. Use the same standard practices as in done in pharmacological trials -- pharmaceutical trials. Put a clinical hold on amalgam. In light of the emerging scientific evidence it's appropriate -- the evidence of risks, uncertainties and harms that we heard about yesterday -- until proof of safety.

DR. JEFFCOAT: You have 40 seconds, ma'am.

MS. MOORE-HINES: Create warnings and contraindication procedures, like with cigarettes. Example: Amalgam may be dangerous to your health. Provide and enforce good clinical practice procedures of informed consent. Dentists should be required to provide brochures or information sheets with objective information about potential harm. It is only fair.

In every walk of life, at crucial circumstances, there is a need for

people of integrity to stand up and take action. I believe that now is such a time in dental history regarding amalgam to resist pressures of vested interests and false assumptions and to stop gambling with people's health. Thank you.

DR. JEFFCOAT: Thank you very much.

We will hear next from Andrew Read-Fuller.

MR. READ-FULLER: Members of the Dental Products Panel, thank you for your time. My name is Andrew Read-Fuller and I'm a fourth-year dental student at the UCLA School of Dentistry. And I am also the vice president of the American Student Dental Association, or ASDA, the largest dental student organization in the United States. And I am here representing our over 17,000 pre-doctoral members, which accounts for approximately 86% of all dental students nationwide.

It is ASDA's objective to advocate for the improvement of dental care and its delivery to the public. And a significant portion of the patients treated by students at dental schools are uninsured. Many are considered to be at high-risk for dental disease based on socio-economic status and level of education. ASDA members are committed to providing care to these patients that is effective, accessible and above all safe.

Student dentists do not have financial motivations in prescribing dental treatment. We don't make any money for the work that we do. And we receive no special benefit to choosing to use one type of restorative material over another. Student dentists are taught to make treatment decisions based on

sound scientific evidence as it supports the FDA's 2009 decision to classify dental amalgam as a Class II device in light of the Agency's conclusion that, quote, "clinical studies do not establish a causal link between dental amalgam and adverse health effects in adults and children age 6 and older." In the absence of new evidence there's no reason to question this conclusion that was reached just last year.

In many instances amalgam is the indicated restorative material for patients in dental school clinics, especially those suffering from rampant debilitating dental disease. Amalgam is strong and durable and is an excellent option to restore posterior teeth or teeth requiring large fillings. In addition, amalgam is less expensive compared to other restorative materials and it helps enable some of the well over 100 million uninsured dental patients in the United States to be able to afford treatment for their dental diseases.

Based on the misinformed belief that dental amalgam is dangerous, many patients in pre-doctoral clinics are now requesting that their amalgam fillings be removed and replaced with composite, even if their existing restorations are intact and replacement is not indicated. As described in the FDA's 2009 ruling, patients are receiving a higher exposure to mercury when amalgam fillings are removed.

ASDA believes that the removal of clinically serviceable dental amalgam restoration solely to substitute a material that does not contain mercury is unwarranted, improper, unethical and constitutes intentional

misrepresentation to the patient.

Student dentists are taught that good communication with patients is critical. I am --

DR. JEFFCOAT: One minute, sir.

MR. READ-FULLER: -- confident in both the safety and the efficacy of dental amalgam and I frequently recommend amalgam fillings to my patients. Like any responsible clinician I explain the risks, benefits and alternatives of any proposed treatment. And I have found that even patients who are initially skeptical of having amalgam fillings are willing to accept them once they understand the facts about amalgam restorations.

I always make sure that my patients are aware of what types of materials are being placed in their mouths before I perform any procedure. I personally have never had a cavity but certainly given the choice between composite and amalgam I would personally request that a dentist place amalgam in my mouth if I had a medium size or large cavity on one of my back teeth. And I would not hesitate to place an amalgam restoration in a family member of close friend.

Eliminating dental amalgam from our dental school clinics would deprive students of a valuable tool --

DR. JEFFCOAT: Ten seconds.

MR. READ-FULLER: -- and would in any instances compromise the quality of care that student dentists can provide to their patients, particularly

those high-risk patients in greatest need of dental care.

ASDA strongly encourages the FDA to reaffirm the safety of amalgam in order to protect the public and enable dental students to provide the highest level of care to their patients.

DR. JEFFCOAT: Thank you.

MR. READ-FULLER: Thank you for your time.

DR. JEFFCOAT: Thank you.

Our next speaker is Christine Bennett. Ms. Bennett? Not here, okay.

We will go on to Sylvia Dove. And you are Sylvia Dove?

MS. DOVE: Yes.

DR. JEFFCOAT: For the record, I just want to make sure don't have people mixed up. Thank you.

MS. DOVE: As an associate at Consumers for Dental Choice, I speak with the parents of children with disabilities and a lot of people who have disabilities themselves. They are concerned about the impact of FDA's amalgam rule on people with disabilities. As a sister of a person with disabilities I share these concerns.

First, FDA already admits that there is no scientific evidence that amalgam is safe for young children and unborn babies. Their developing neurological systems are especially susceptible to the neurotoxic effects of dental mercury, according to FDA. How much more risk is there for a child who

already had a neurological disability? FDA admits that it does not know. But the Agency so far has taken no steps to protect this most vulnerable population.

Second, most of the world, including the United States, recognizes the right of individuals to make their own treatment decisions for themselves and for their children. It's a basic human right.

The disabilities community particularly values this right. For decades people with disabilities were institutionalized by doctors who deprived them of their ability to make their own decisions about their own bodies. And now, apparently with FDA support, dentists continue this long tradition.

Throughout the 2009 dental amalgam rule, FDA insists that consumers do not need any information about amalgam's risks or about amalgam's mercury content because dentists can, quote, "make treatment decisions for their patients." This phrase has emboldened dentists across the country to openly violate parents' rights to make treatment decisions on behalf of their children with disabilities.

Since FDA's 2009 rule I've watched a dentist representing the Philadelphia County Dental Society openly gloat about how he denies treatment, even basic tooth cleanings, to children with disabilities when their parents refuse mercury and exercise their right to ask for composite.

I have spoken with a mother from North Carolina who has three children on the Autistic spectrum. She was turned away by the only dentist in her area simply because she did not want to subject her neurologically impaired

children to this neurotoxin.

The disabilities community has vocally spoken out against FDA's position on amalgam. Dr. Chet Yokihama is co-founder of Aiding the Medically Compromised, a non-profit that promotes dental care for the disabled. He confirms that amalgam is not necessary for people with disabilities. Composite fillings can be placed, even under general sedation or IV sedation, by a competent dentist.

Similarly, the Pennsylvania Governor's Advisory Committee on Disabilities has passed a resolution condemning dentists who refuse treatment to people with disabilities when they exercise their right to choose composite over amalgam.

DR. JEFFCOAT: One minute, please.

MS. DOVE: FDA needs to consider that there is no evidence that mercury fillings are safe for people with disabilities. And FDA needs to immediately retract its offensive claim that dentists have the right to make treatment decisions for patients. We make our own decisions about our bodies and we don't need any dentist to tell us how to do it. And I don't know any informed consumer or parent who willingly chooses mercury. Thank you.

DR. JEFFCOAT: Thank you.

Our next speaker is Marie Flowers, who I believe is coming from the back of the room.

MS. FLOWERS: I'm Marie Flowers and I'm here today

representing the 100,000 people who have contacted DAMS, Dental Amalgam Mercury Solutions, over the past 20 years seeking help for mercury poisoning.

I'm a coordinator for DAMS in Virginia and have the website mercurypoisoned.com. I tell how my dentist poisoned my brain in 2001 when he partially drilled out only one mercury dental filling and let me breathe the mercury vapor. Nine days after my dentist drilled into the mercury filling my brain starting vibrating violently inside my skull like it was trying to jump out. My brain was on fire, and I had electrical charges surging up and down my body. These charges are called by neurologists Lhermitte's phenomenon. I call it mercury hitting the brain.

Many people who have contacted DAMS can't be here today because they are too sick or too poor or at home trying to work off all the thousands they have spent on medical and dental bills. People spend thousands for dental restorations and then find out they have to redo the whole thing over again because it's so toxic it's making them ill. But some cannot even work any longer and they're trying to get their disability. So these are the poor folks that can't show up. And then some are dead.

A young woman called me several -- didn't call but she e-mailed me several years ago. She was confined to bed. Her throat was paralyzed; she couldn't speak. She was perfectly healthy until a dentist took out 12 mercury fillings without using any special protection for her. In a short time she developed Lou Gehrig's disease. She is probably dead now since these patients

don't live to be very old.

Other people that have contacted me is a man who was unable to follow through to find a dentist and a holistic doctor and he was so depressed from the affects of mercury he committed suicide. A young college student called me who was losing his memory. A dental student in Virginia contacted me saying he was loosing his ability to function. A registered nurse called to find out why she had severe heart palpitations after her dentist removed some fillings and the cardiologist couldn't even figure out what the problem was.

Lee Cashman, our executive director, hears these stories all day long. He's on the phone 10 hours a day, 7 days a week talking to people that are poisoned. He spoke to a instructor from a community college in Virginia whose dentist placed gold crowns over top of mercury fillings. This combination of mixed metals: gold, sliver, zinc, tin and mercury acted like a battery in his mouth causing more mercury to come over the fillings. Though Rob initially improved after having his fillings removed, the damage was so severe he had to retire prematurely from teaching because he developed Parkinson's disease.

Welders know you don't mix certain materials together. Bridge builders know that. But dentists don't know that. Why aren't you professors in these dental schools teaching these people something so they don't come out and poison people? Why aren't you teaching them not to mix metals in their mouth causing the galvanic currents?

DR. JEFFCOAT: One minute, please.

MS. FLOWERS: But yet you get on the ADA website and all they say is it's another allergy.

My dentist mixed metals in my mouth. He also exposed to me to mercury vapor. I was shocked at the ignorance of the dental profession. And so what gets me is why should people get on a phone and call a housewife in Virginia to find out they've been poisoned by their dentist? Why can't they trust the dental profession? And it's because --

DR. JEFFCOAT: Thirty seconds, ma'am.

MS. FLOWERS: -- of the ADA curriculum that's being taught. It is so substandard and it is so archaic dentists are poisoning people every day and giving them neurological diseases. You people need to bring the standards of care up. Contact the IAOMT; they will teach you how to properly take fillings out of people's teeth. Thank you.

DR. JEFFCOAT: Thank you.

Our next speaker is Katina - is an "R" missing from that? Is it Katrina or Katina?

MS. MINNEY: No, it's Katina.

DR. JEFFCOAT: All right, Katina Minney.

MS. MINNEY: All right.

DR. JEFFCOAT: Thank you.

MS. MINNEY: I'm not going to cover a lot of the technical stuff because I don't have enough time and I think that professionals have done that

pretty well. I came all the way from Oklahoma at my own expense for this.

My husband has mercury toxicity. He was September 2002 completely healthy 33-year old man, worked all the time, no drug use, had a house full of kids, workaholic, religious, doing very well. We were at the top of the world, you know. In August 2002, he had amalgam fillings placed. By October 2002, he had atrial fibrillation that he was hospitalized for, no cause; they couldn't figure out why.

2003 that continued, the A-fib. All the medications for it. Chronic fatigue, tremors. 2004 he got a -- he had some teeth pulled, more dental work. Got a deep vein thrombosis in the left leg, unknown cause; they didn't know why. He didn't injure himself.

2005 he had an empyema in the right lung. He had to have a thoracotomy, 2 weeks in the hospital, almost died. 2006, loss of vision, shaking, falling down, confusion; unknown causes. His mind started going. We went to every specialist under the sun. Hundreds of thousands of dollars in medical testing trying to figure out what was wrong with him.

2007 he again went into A-fib, had to have cardioversion. 2008 he underwent pulmonary ablation to try to fix the heart problems that were going along with everything else.

March and April 2009 he had additional dental work done. And by the mid-April 2009 he was on is death bed again. He couldn't hardly get out of bed. He was shaking. His skin burned to the touch. He had a migraine every

single day for over a year.

We went to the Mayo Clinic. We've tried every specialist in our area. We're in Oklahoma. I'm an RN. We've been to every doctor under the sun. I had studied, studied, couldn't figure out what was wrong with him. Everything was normal; they don't know why he kept having all these symptoms. Mayo Clinic, 2 weeks, $80,000, still no answers. All the tests come back normal; we don't know what's wrong with him.

We come home. We have six children and we come home to die. That's what it was. My husband could not get up and get take my kids places. He had vision loss. He couldn't hardly drive. It was horrible. It was horrible.

May 2010, I had had somebody say something to me about dental fillings. I thought, well, that can't make you sick. I've never heard of such a thing. I'm a nurse, public health nurse, never heard of amalgam fillings making people sick. Looked it up and all the symptoms were there. I was dumbfounded. Called our doctor, had him do heavy metal urine testing. The next day we went and started having fillings taken out safely and -- before we even got the results. And he --

DR. JEFFCOAT: One minute, ma'am.

MS. MINNEY: -- immediately started improving.

Today, my husband's probably back to about 50, 60% where he was 6 months later with chelation therapy and filling removal. He also was led toxic from his job and I guess when they put the fillings in we didn't know he was

lead toxic. That exacerbated it and it what made him so ill.

What I want to know is why we're not telling people we're putting this in their mouth? At the very least why are we not telling people "We are putting mercury in your mouth"? I'm a public health nurse, I didn't know.

DR. JEFFCOAT: Thirty seconds, please.

MS. MINNEY: None of the doctors I went to knew. You know, we all know it's in immunizations. We have informed consent there. Why is there not informed consent to have mercury put in people's mouths? The dentist facility I worked at didn't even know it was 49%. Don't they read the bottles? I read the bottle to everything.

I think that the FDA has a responsibility to the people to take care of this situation. Thank you.

DR. JEFFCOAT: Thank you. Thank you.

Our next speaker is Karen Burns.

MS. BURNS: I'm going to keep it short and sweet. I testified in 2006. I had the same thing that everybody else back there has. I was a dental assistant for 24 years until I couldn't work anymore. I lost my job. I can't work anymore. I get $700 a month in disability and I have to pay my own way to come here to remind all of you that you're here for the public, you're here for the worker.

I shouldn't have to do this. I appreciate you people all here for coming and making an attempt because, you know, if you listen to the news you

realize the FDA has been having trouble, you know, between Vioxx -- Avandia, that really shocked me because that was bad 4 years ago, 5 years ago.

It's time to do your job and protect the public, protect the workers, protect the pregnant women, the children under 6 years old, that it says right on the amalgam bottle that you cannot give a child under 6 years old an amalgam filling. It's time. We can't do this anymore.

In 2006 there were people here in wheelchairs, a woman that couldn't take of herself and all's I have to wonder is are they still alive? What happened to them?

Suzanne, Dr. Runner over here quoted in the newspaper that 142 adverse affects were reported. There were 2,000 in '06 reported on your website. She said when I called her that she remember the 2,000 and you kept it in your plans when you were trying to go over that White Paper, whatever happened to that I don't know. It's got to stop. Look at everyone's faces, look at these people, look at that woman with six kids whose husband couldn't even go to work anymore; how could you look at these people and keep doing the same? Thank you.

DR. JEFFCOAT: Thank you.

Jim or James Mody?

I believe he checked in. Not here? Okay. I'm just going to just call the other people who weren't here at the time I called them. Holly Harvin? James Cooper?

Excuse me, are you reading for some -- well, I'm -- are you reading for James Cooper? Yeah, I'll get there. I'll get there. Okay. Given the bad weather we just want to give everybody a chance to the best of our ability. And Christine Bennett? Okay, and James Moody is -- Mody is not here.

Okay, now I'm opening the floor for other people who may have, since we have some time, who would like to speak and you would -- yes, they will have 3 minutes.

And you are welcome -- ma'am, may I have your name? If you -- you already spoke.

MS. KERGER: Yes, I just --

DR. JEFFCOAT: You want to speak again? Okay, you have 3 minutes.

MS. KERGER: I was talking about Alzheimer's disease and the relationship between mercury and dental fillings. Recent research by Dr. Jay Mutter and Dr. Richard Deth identified the correlation between mercury exposure and Alzheimer's disease. Those studies were submitted to this committee.

Should we not consider how many Americans have a genetic predisposition not to be able to excrete mercury from fillings? Do dentists test their patients for the ApoE genetic predisposition prior to placing dental amalgams? How do dentist check for so-called allergies to mercury? Mercury's not an allergy.

Based on millions of Americans with amalgam fillings -- and the undetermined numbers who many very well be prone not to be able to excrete the absorbed mercury from fillings and known vulnerability of mercury to the fetus, young children and those with kidney disease, I implore the FDA to do the right thing.

As an injured consumer and director of the Pennsylvania Coalition for Mercury-Free Dentistry I asked FDA to use a precautionary principle as Norway, Sweden and Denmark has done. Those three countries have banned the use of mercury to protect their citizens.

I ask the FDA to protect the American people rather than industry. I ask the FDA to stop this crime to humanity. I ask FDA to ban the use of mercury fillings now, rather than later. And please, please listen to everybody who testified at this meeting. It's extremely important. They're just not anecdotal stories.

DR. JEFFCOAT: One minute.

MS. KERGER: They're real lives that have been injured. And the physicians and the dentists and the scientists who have spoken here today know what they're talking about. They are relying on scientific peer reviewed studies You can't shove them under the carpet any longer. We want a healthy America. We're not going to have it if you continue to endorse the use of mercury in dentistry. Thank you.

DR. JEFFCOAT: Thank you.

Do we have any other? Okay, we have how many people who want to speak so that we can divide by the amount of time? One, 2, 3, 4, 5. Okay, you have 3 minutes.

DR. KENNEDY: Thank you. I'm Dr. David Kennedy. I'm a past president of the International Academy of Oral Medicine Toxicology and mercury doesn't bother Kennedys. My grandfather lived to be 93 years old and he graduated from University of Pennsylvania in 1875. And -- no, 1895. And my father graduated in 1938.

Mercury doesn't bother Kennedys and that doesn't make it right to put it in people that you saw here talk today. It also doesn't make it right for the dental students who are taught that mercury's safe to argue their patients into having mercury. That's what we were taught in dental school.

We got a perfect discussion yesterday about how we don't use the "mercury" word; oh, we call it amalgam. That's part of the deception so that people don't understand you're implanting them with a time-release implant that will accumulate in various organs. Whether we can prove it's above the reference dose or below the reference dose doesn't make any difference. The reference dose is the ceiling above which we don't want to go.

What happens if your mercury dose is down here? That's a good thing. Not a bad thing. On YouTube you can watch "Safer Amalgam Removal." The American Dental Association protocols were used in 1990 and they showed a huge spike. When this committee voted to reject the White Paper in 2006,

Rodway Mackert was quoted in the *Wall Street Journal* saying it's unsafe to remove amalgam. Well, gee golly, how come it's so safe to put it in and it's dangerous to take it out? I don't understand.

Doesn't that kind of ring like maybe there's some falsehood going on here? I say there's a lot of falsehood going on here. You can remove these things safely if you follow the Occupational Health and Safety Engineering Controls and work practices. We went to OSHA in California and said we need masks, vacuums, protection and they came back and said all of that is required by the law. No dental school in the United States follows these protocols and it is the law; not for schools but for every practicing dentist in the United States --

DR. JEFFCOAT: You have 1 minute.

DR. KENNEDY: -- it is the law. Why are dentists not following the law? They're taught criminally by their dental school because it is a accredited by a trade association that has a vested interest in this material. That's inappropriate. And that if you really believe in the professional ethics that we've all signed on to, you will follow protocols required by law that stop that blood spike of mercury that was proven in the scientific literature by the Frykholm experiments in 1957 with radioactive mercury. That can be prevented. That should be prevented. Please, God, insist upon the dentist following --

DR. JEFFCOAT: Fifteen seconds.

DR. KENNEDY: -- reasonable protocols. Thank you.

DR. JEFFCOAT: I would like to remind people if we can keep the

decibel --

Next speaker, please state your name.

MS. GALLAGHER: Hi, I'm Kelly Gallagher.

Distinguished Panel, thank you very much. I'm also a victim of mercury poisoning. I was an athlete and a scholar. As a child I received 17 mercury fillings from age 9 to 19. By 20, I was diagnosed with Hodgkin's lymphoma. Since then I've gone through mantle radiation, 14 months of chemotherapy, a stem cell transplant, four pacemakers and most recently a new aortic valve. So I commend the FDA on a lot of your devices; I think they've worked and thank you very much. I've had 100 blood transfusions and 13 catheters. But the 17 mercury fillings have really done a number. And I've been following this issue since 2001 with a camera and I can tell you that it's insanity.

In 1976, the *Journal of the American Dental Association*, the whole story was about the toxicity of mercury in their own dental offices. I suggest that -- I don't have it with me but we should get it to all of you.

According to Webster's Dictionary, mercury is a poison. And also according to Webster's Dictionary a poison is something that can cause death. So my question is, you know, there's many, many smart doctors, scientists, toxicologists and professionals that have testified everywhere from California Dental Boards to government reform hearings, so my question is if somebody knowingly poisoned someone are they guilty of premeditated manslaughter? Because that's really what we're looking at here. People are dying while we're

pushing paper around.

I've been to the United Nations. I've been UNAP. I've been to every government forum hearing. I've been to so many California Dental Board hearings it makes me sick. And on my own dime, too. Because I made a promise to God when I thought I would croak having a bone marrow transplant, if you let me live I would do whatever, and I asked God to send me signs. I did not know it was going to be about a sign hanging in a dental office and that's how it started.

And here we are again.

DR. JEFFCOAT: One minute, please.

MS. GALLAGHER: So I just -- I really hope that you'll listen to all these testimonies and go in your heart. Mercury's toxic. We all know it.

DR. JEFFCOAT: Thank you, please. Thank you for your presentation.

Next speaker, please state your name?

DR. MARKUS: Steve Markus, again. I'm going to wrap up what I would have wanted to say if I had been granted more time.

I addressed this Panel back in 2006. I had the opportunity to write my talk after having listened to all the testimony on day one and what you're going to hear right now are just some paragraphs from what I had to say back then.

You know, one of the things I think that's important is erring on the side of caution. When I was student at the University of Pennsylvania my

mother used to send me articles from the *New York Times* because I was reading the *Inquirer* and that wasn't good enough for her. So most of those envelopes went right into the circular file, but one particular weekend I had time. And if I hadn't seen anything about the Vimy study in the *New York Times* I might never have -- it changed my life because after having read about the sheep study with the radioactive isotopes of mercury distributing to all aspects of the body, that was the last day that I ever placed mercury fillings. Now, that occurred after I was in dental school, around 1990, but those articles from the *New York Times* continued to come from 1971 and they still continue to come.

I began thinking about the storage of mercury scrap at that point in time and how the ADA told us to store it in a sealed glass jar under antifreeze or the high specific gravity fluid. But the ADA told dentists out of the other side of their mouth that the mercury became inert once placed. So why did it eat a hole through the lid of the bottle?

I thought about the environmental impact of all the mercury that was going through my suction and out through the sewer system. I installed a separator on my building and now every year we probably recycle 3 to 5 pounds of mercury that would otherwise hit sewage treatment plants.

There's something in here -- because I'm just -- I'm going from something on the web right now where I have my speech. Pro-mercury dentists argued yesterday, which would have been 6 years -- 4 years ago, that composite fillings are less durable, that dental schools can't teach it. This is all ludicrous.

Dental schools teach dexterity and technique. They also insist on the use of the rubber dam. It's not the training of the students; it's the retraining of some of the dinosaurs that may still be teaching that is the obstacle.

The image of the fighting, screaming welfare child is the exception and not the rule. It's certainly not the reason for you to approve the use of mercury in children's heads, a substance that has no known --

DR. JEFFCOAT: You have 20 seconds, sir.

DR. MARKUS: -- half-life.

Okay. And one of the things that was asked was, what was the cost impact? A gentleman from Delta talked about the cost impact today and I would propose to this Panel that you consider what the cost impact is to the medical system as it stands now with all the untreated problems that are a symptom of mercury toxicity --

DR. JEFFCOAT: Sir, please wrap it up.

DR. MARKUS: -- that the MDs don't even know about.

DR. JEFFCOAT: Thank you.

Thank you, and please state your name because --

MS. MOORE-HINES: Sarah Moore-Hines, wrap up.

DR. JEFFCOAT: Thank you.

MS. MOORE-HINES: Very quickly, as perspective I understand that around 2002, maybe FDA can correct me on the date, the FDA recalled a horse salve called Miracle Leg Paint. The salve was for horse blisters and they

recalled it only because it contained mercury. So when the FDA discovered that this -- and I'm a horse lover by the way -- that it contained mercury their position was, we don't have to show that it harmed horses, only that it contained mercury, and it was recalled. So can we use that as a precedent when we're thinking about thinking about the unborn little children, adults and families?

This is a time to act wisely, in an informed way and courageously for the sake of countless Americans. Please take heed. Thank you.

DR. JEFFCOAT: Thank you very much.

Yes, sir?

DR. NUPPONEN: Hi, I'm Dr. Pentti Nupponen, I'm the quack, remember?

First to the dental student here. I would like to talk to you 35 years from now when your feet feel numb, your hands tingle, you can't hear anymore, you can't see anymore. You will remember this time but I know I will not be here.

One of the really important things is today that you perhaps --

DR. JEFFCOAT: Excuse me, may I ask that the speakers address the Panel and not other speakers because --

DR. NUPPONEN: Okay.

DR. JEFFCOAT: All right.

DR. NUPPONEN: One of the things that we need to remember that you are the ones who recommend what comes out of this hearing these last

2 days. Remember, 765 composite -- materials are available to dentists today to replace the amalgam fillings. We have countless number of patients that we have helped -- the quack has helped. The countless number of patients, addition to the several that I mentioned to you.

Every other month I hear from a dentist who have blown their brains out; they are dropping dead left and right, sometimes even already in the dental school. It is important to realize that the mercury goes through the placental barrier, goes through the brain cell barrier without any trouble at all. Difficulty sometimes comes of trying to retrieve the mercury and get the patients feeling normal again. That's why the neurological diseases that are associated with the mercury are the ones that are most devastating to the patients.

You, the Panel, are responsible to make a recommendation to FDA and you could stop the suffering of millions of people, not only United States --

DR. JEFFCOAT: One minute, sir.

DR. NUPPONEN: -- but around the globe. You can make medical history today. World is watching you. If you vote to continue the status quo shame on you. Make your decision with your heart not with your wallet. I love to be the quack dentist because we save patients lives.

I wonder how the other dentists would feel if they would just one time see what I see every day?

DR. JEFFCOAT: Thirty seconds.

DR. NUPPONEN: Thank you.

DR. JEFFCOAT: Thank you.

Is there anyone who hasn't spoken who would like to speak?

MR. REEVES: Yes. I'm Robert E. Reeves. I'm an attorney, my name's on the petition along with Jim Love's.

DR. JEFFCOAT: Yes.

MR. REEVES: I regret to say this but I basically consider the FDA a corrupt agency. If you look at the history of it, the FDA seems to work for the clients, by that I mean big business and not for the public.

But what I want to say really is to try to sum up why this is such a difficult issue. Dr. Kennedy said, "Kennedys aren't bothered by mercury." Dr. Kennedy wasn't bothered by mercury, his father wasn't, his grandfather wasn't. That has to do with genetics.

There are three things that are going on here. One is exposure can be highly variable. Two, genetics are highly variable. And three, the symptoms are highly variable. It makes it very hard to understand this.

Exposure can be highly variable because -- I'm old enough that I had low copper amalgams, emit one-third as much mercury as the high copper amalgams you dentists now use. Why that occurred I don't know. As far as I know it's not published, but James Adams at the University of Arizona has done studies on this. I've urged him to publish it and he has not.

In addition, you have cumulative toxicity from other sources.

That's what part two of Richardson's study is about, if you want to read it. It's detailed.

You have fish from mercury -- excuse me, methylmercury from fish; you have other environmental exposures, and this is by far the largest exposure. In addition, you have cumulative toxicity and synergistic toxicity. Boyd Haley put up Schubert's paper, 1978, but didn't really talk about it. But Schubert's paper talks about the high synergistic toxicity between lead and mercury. And we are lead-exposed population because we put lead in our gasoline and lead in our paint of years. And anyone who's my age or even considerably younger --

DR. JEFFCOAT: One minute, sir.

MR. REEVES: -- has lead exposure.

Then you have the genetics, and I may want to take an extra minute if I can?

DR. JEFFCOAT: No, sir. I'm sorry.

MR. REEVES: All right. You have --

DR. JEFFCOAT: You have people who haven't spoken at all.

MR. REEVES: Well, you're taking up my time now.

You have seven genetics that deal with this issue. ApoE has already been mentioned. I'm ApoE3/4. If I was 4/4, I probably wouldn't be speaking to you because I probably would be dead by now, but fortunately I had some removal capacity in that system. But you have G6PD, CPOX 4, MTHFR that

I know of, and I'm a lay person.

Then you have the myriad of symptoms. This can cause any kinds of symptoms. You've already heard that. If you will go --

DR. JEFFCOAT: Fifteen seconds, sir.

MR. REEVE: If you will into the petition at page 25 you can read the neurological symptoms and the data that's there, the peer reviewed studies that relate this to neurological symptoms, varied neurological symptoms.

Susan Runner has said in the past --

DR. JEFFCOAT: Sir, you need to finish --

MR. REEVES: This is my concluding sentence.

DR. JEFFCOAT: -- up. Okay.

MR. REEVES: This is my concluding sentence.

DR. JEFFCOAT: You're -- yeah. No, no, I -- we're finished with time. There's a gentleman in the back who has not spoken. I do not know your name, but if you will come up and say your name, sir, we'll be happy to hear from you.

DR. COOPER: My name is James N. Cooper, D.D.S. I was on the schedule. I just arrived.

DR. JEFFCOAT: Okay.

DR. COOPER: I'm a practicing dentist in Philadelphia, Pennsylvania. I would like to give my thoughts on the subject of the use of dental amalgam.

My work history has included nursing homes, state mental hospitals, public health clinics, and the correctional setting. I now focus my practice on serving in an underserved minority neighborhood. Due to diseases endemic in the inner-city, poor diets and lack of access to care, dental caries and tooth loss due to dental carries is highly prevalent in the patients I treat.

Xerostomia due to diabetes, side effects of medications used to control high blood pressure, heart disease, and mental illness, the use of illegal drugs like cocaine, methamphetamine, cannabis and tobacco smoking make many of my patients a challenge to rehabilitate.

My patients with HIV and Hepatitis C often prevent deranged immune systems incapable of weathering the constant assault of caries causing pathogens. Often the only restorative material available to me that allows me to possibly salvage their ravaged dentitions is dental amalgam. The silver content with its toxic effect on bacteria, viruses and fungi and the mercury content with its antiseptic properties allow me to save teeth I would otherwise have to extract.

As most of my patients have government-sponsored health insurance, cast metal and porcelain restorations are not available to them, nor do they have the resources to pay for them as an option. Composite restorations are technique sensitive, time consuming to place, and studies have proven do not last long. This will place, excuse me, a financial burden on federal Medicare and state Medicaid budgets as these restorations are unreliable, and

that is the composites, and will have to be replaced more often in the above-mentioned populations I treat.

In closing, the loss of the use of dental amalgam in dentistry will cause an increase in tooth loss, an increase in the dentureless patients, and an increase in government expenditures hurting the already underserved. Thank you.

DR. JEFFCOAT: Thank you.

Do we have anybody else who hasn't spoken yet? Okay, you go first, then you, and then I think we will be -- we're done with time for the open session.

MR. ROBERSON: Hi, my name is Allen Roberson. I'm from Philadelphia. I'm a parent. I'm down here with my wife, Judy, on our own dime.

When she was 3 months pregnant we -- well, she had amalgam replaced in four of her teeth and a crown put on. We've heard enough stories. Our daughter is disabled. Some cost savings.

We've got a big list of medications that she's on and she's on disability. I think not having the dental work done at all back then would have been terrific. It could have waited until she was at -- until Emily had been born. We did not know anything or never told anything about the mercury that was in the amalgams. This is criminal. Some cost savings. She's on disability now. She's still alive; that's wonderful.

I have to work very hard not to hate the people who did this to

my daughter. I've been successful at that but I have to work at it. Please, do your job, represent the people and not the trade organization. I know these people over here want to feel good about what they do. I'm talking about the heads of the Dental Association. I work hard not to hate them. They want to feel good about what they do serving the public, helping people. Help them. They're poisoning themselves, too. I really do think it impairs their thinking. Thank you very much.

DR. JEFFCOAT: Thank you, sir.

We have one last person who hadn't spoken yet, thank you.

MS. TEMOWSKI: My name is Patricia Temowksi. I'm a member of the public. I hadn't intended to speak to today so I'm not totally prepared.

First, let me thank the esteemed Panel for coming together and listening for 2 days. However, as a member of the public I respectfully and officially challenge the credentials of the voting members of this Panel that I just read today and yesterday as being qualified to make a medical decision. I noticed that you are dentists, making a medical decision as to the safety of dental amalgam fillings. I was told that dentists are not supposed to practice medicine without a license and yet you are clearly making a medical decision.

However, if it is determined that you are legally able to make this decision I hope you will listen to overwhelming scientific evidence and overwhelming public evidence that mercury amalgams are dangerous, not the biased propaganda by the ADA.

You dentists sitting behind me have been brainwashed since day one of dental school. It has been drilled into your heads that mercury amalgam is safe and I am appalled that you people can possibly sit here for 2 days and think that this poison is safe.

And to the dental student open your eyes. Just because you had been told 1,000 times in the last 4 years that mercury is safe in your mouth, does mean that it is safe?

DR. JEFFCOAT: Please --

MS. TEMOWSKI: You have been brainwashed.

DR. JEFFCOAT: Please address your comments to the Panel and not to any particular member --

MS. TEMOWSKI: Okay.

DR. JEFFCOAT: Okay.

MS. TEMOWSKI: Anyone in the public or dentist or Panel may be a great mercury excreter and never feel the symptoms of mercury in your mouth. But do not think for second that you are not being affected. The only safe level is zero. How can you think that 1 to 3 micrograms of mercury per day is safe? Given the high levels of other toxins in our environment, zero levels of this poison, mercury, is safe. And all common sense will tell you do not put mercury inches from the brains of ourselves and our children.

My dentist told me mercury is safe and stronger and would last longer than composite and stupid me believed him. Well, let me tell you a

mercury amalgam caused a crack in my molar because of expansion that would not have happened with a more stable composite filling.

I have a grandmother who died of Alzheimer's, slowly losing her mind over a period of time until the last few years of her life she was in a fetal position in a nursing home not recognizing anyone, having to be fed by her nurses. My 80-year old mother is currently in a nursing home diagnosed with Alzheimer's and my sister who is in charge of her medical care believes the ADA propaganda and refuses to have the mercury in her mouth removed, which is by the way interacting with the gold her in mouth. The doctor at the nursing home was trained 35 years ago and is similarly brainwashed by the ADA, not a medical body, telling him that they are safe.

I had a job as a software engineer at a large corporation. At the age of 42 I had to stop coding because I could no longer handle the 20 lines of logic in my head and it was taking me all day to write code that I used to be able to write in a couple of hours and all week to write code that I used to be able to write in a day or two.

DR. JEFFCOAT: One minute, please.

MS. TEMOWSKI: I used to be able to code faster than my 30-year old colleagues, now I was much slower.

My dentist of 20 years who placed my amalgam fillings does not know that it have neurological symptoms related to mercury fillings. This dentist, who I no longer go to, does not know that the mercury and lead levels in

my body are several times the maximum exceeded safe limits. No wonder I couldn't think. This dentist does not know that 2 years ago I was so neurologically challenged it took me 4 hours to write a paper bill because I couldn't find the envelope, the stamp, the bill, the payment, the pen, my bank account levels all at the same time; it was just too many tasks to handle at once. This dentist does not know that I experience anger and emotional outbursts because of mercury poisoning.

DR. JEFFCOAT: Please wrap it up, you've got 10 seconds.

MS. TEMOWSKI: You dentists do not know that you are killing your patients or yourselves. You are slowly but surely killing them every time you place a mercury amalgam filling. Wake up. You've been brainwashed for 4 years of dental school. Every month when you read the brainwashing propaganda of the ADA. And --

DR. JEFFCOAT: Ma'am, thank you. Thank you, we really appreciate your presentation.

All right. I really want to thank the members of the public. The Open Public Hearing is now closed.

Are there any questions from the Panel to the members of the public who presented today? Yes, sir.

DR. DOURSON: Just one. Mike Dourson, question to our dentist colleagues that have testified. Regarding the toxicity of composites, I heard somewhere we had 765 composite fillings; do we have any toxicity on some of

these composites, please?

DR. KENNEDY: Yes, Mark Richardson discussed that in his paper yesterday that the Academy of Oral Medicine and Toxicology has done repeated risk assessments on this dating back almost a decade of so. The components in composites, some of them are not very friendly. When you look at -- and he showed you a slide, that when you look at the risk levels -- excuse me, when you look at the risk levels, the risks of exposure are considerably below the reference dose and the reference concentrations.

Interestingly enough, the composites, in order to get approved, they were invented after the FDA was formed and so the FDA correctly required the manufacturers produce evidence of safety and they passed the biocompatibility tests. Amalgam will not. So there you are.

But yes, there is -- there are several risk assessments on that. You can access it on our website or Google it.

DR. DOURSON: Thank you.

DR. JEFFCOAT: Thank you. Yes?

DR. WHITE: I have a comment and then a question.

First, we've heard from a number of patients who have received mercury fillings who felt compelled and passioned to come and present information and I want to just acknowledge that I hear them as a Panel member. I got explicit notes and as a clinician who teaches in a dental school I can assure you that I'm not a dinosaur when it comes to teaching dentistry. And I believe

most of my colleagues are not, as well.

What I'm questioning, what I would like to see is from this compilation of case studies, there are a number of factors that keep bubbling to the surface and I'm wondering if the IAOMT or DAMS or someone has actually put together a composite -- not a composite restoration but a composite profile of the subgroup, and it's clearly a subgroup of highly sensitive individuals where amalgam is contraindicated, and for me I'm wondering if there's a classic or a combination of histories that would help guide the profession and help guide FDA in its labeling.

So I'm -- you know, I heard something on genetics, the ApoE, and there's a genetic profile, there's a history profile; I'm wondering if there's a composite that has been formed that says this group of sub-patients amalgam would be contraindicated for, for instance?

DR. JEFFCOAT: And that's Dr. White who spoke.

DR. WHITE: Thank you.

MR. REEVES: I'm Bob Reeves. I'm one of the people that talked about genetics. I don't think that that has been done. I don't think it would be very easy to do. but there are a huge number of variables.

One of the things I didn't mention was the exposure that you get on replacement of amalgams. So you've got this huge exposure variable. Do they have the old low copper? Do they have high copper? Do they have other metal s in their mouth which definitely are going to increase the disposition of

mercury and the intake of mercury.

DR. JEFFCOAT: Sir, in the interest of answering the question --

DR. WHITE: Yeah, I --

DR. JEFFCOAT: -- the answer to the question is there is a composite --

MR. REEVES: There is not a composite.

DR. JEFFCOAT: -- data available or there are not?

MR. REEVES: What I'm doing, Madam Chairman, is explaining why there's not a composite, if I may do that?

DR. JEFFCOAT: You may do that very briefly.

MR. REEVES: So you've got the exposure. You've got the genetics, and there are seven genetic variables. And I think we have Echevarria and Woods and everybody else who's done genetics here, there wouldn't be -- we would have a 5-day conference with lots of questions and no real answers.

So it would be very difficult for you as a practicing clinician to get to the bottom of the genetics. But you could start with ApoE. But, you know, do we really want to be doing ApoE testing and finding out that we can put it in people with 2-2, which have lots of cysteine,- four cysteines. I only have one cysteine.

DR. WHITE: I'm just --

DR. JEFFCOAT: Okay.

DR. WHITE: -- just looking for --

MR. REEVES: Okay.

DR. JEFFCOAT: A simple answer.

DR. WHITE: -- something that might make life easier for me and everybody else.

MR. REEVES: I understand. Dr. Kennedy's going to speak more to that.

DR. KENNEDY: Well, actually, you're actually asking us a question that the FDA is the only agency in the United States that actually can answer. You have the funding; we don't. All of the studies that we've done have been funded privately out of the pockets of our members. And that what you're asking is what -- the question that should have been asked 50 years ago. And we will be glad to answer that for you. Please find a grant for us. Thank you.

DR. JEFFCOAT: I am going to request that you do not recognize people to speak, that needs to come through the chair. Otherwise they cannot keep track of who is saying what.

Do you -- have you had a sufficient answer to your question, Doctor?

DR. WHITE: Yes.

DR. JEFFCOAT: Thank you.

Do we have other questions?

(No response.)

DR. JEFFCOAT: Okay. We will now have a short 15-minute break.

Panel --

MS. TEMOWSKI: You said you -- the question is do you have a bunch of case studies --

DR. JEFFCOAT: Ma'am, he said --

MS. TEMOWSKI: -- and little statistics --

DR. JEFFCOAT: -- his question was answered.

MS. TEMOWSKI: Okay.

DR. JEFFCOAT: Ma'am, no. I -- we -- excuse me, you're out of order. You're out of order, please -- please have a seat, okay?

If we don't get to what the FDA has charged us to do today you will all have wasted your time and money in coming to address us. So I'm trying to make sure that doesn't happen.

We are now going to have a 15-minute break. Panel members, please remember do not discuss the meeting topic during the break amongst yourself or with any members of the audience. Don't even make phone calls about it. We will resume at 10:25 promptly. Thank you.

(Off the record.)

(On the record.)

DR. JEFFCOAT: We need the Panel to convene. If any members of the public want to speak with each other they do need to do it in the hall. May we have everybody seated, please? May we have everybody seated, please?

We will now hear a brief recap from Mr. Watson of the FDA.

MR. WATSON: Thank you.

DR. JEFFCOAT: Thank you for your brief recap.

MR. WATSON: I'm Anthony Watson. I'm the director of the Division of Anesthesiology, General Hospital, Infection Control, and Dental Devices. I'm going to give a brief recap of what we've heard over the last day.

I just want to put a couple things out there. This is my interpretation of what I heard. I'm not a transcriptionist so there could be some error in what I'm saying. If I miss the point, I tried to pick some -- there were very dense presentations yesterday with a lot of information. I tried to pick out the bullets, what I heard was important points. So unlike the very fluid speakers yesterday it may sound a little disjointed because I'm just trying to pick out the important points.

First thing that happened yesterday was that we gave a summary of -- FDA gave a summary of the regulatory history of dental amalgam. FDA and other agencies have tried to tackle the safety of dental amalgam for the better part of the last two decades, culminating the recent final rule for a classification in 2009 and the petitions which are the subject of this 2-day Panel.

The petitioners then summarized their individual petitions. The first petition was from Misters Love and Reeves; that's their first petition. We heard in that petition that they had pointed out that there was a campaign of obfuscation and deception by pro-mercury advocates. There was a study discussed that reported a significant correlation between mercury dose and

urinary porphyrins. Meaningful clinical data would likely require a decade's long study is what we also heard.

Dr. Edlich's petition requested that FDA require informed consent for placing amalgams and he pointed to labeling, vaccine labeling as a possible model for that. He also recommended that amalgam be banned.

The Turner petition discussed animal data, particularly when it came to monkeys and showed that mercury levels in monkeys with amalgam are higher than levels allowed in fish. There are techniques available to assess the affects of mercury on cell biology. And mercury exposure is a major contributor to disease. Also pointed out that the law requires an affirmative demonstration of safety and not just the absence of negative outcomes. The FDA website needed to be updated and clearly navigable.

The second Love and Reeves petition talked also about requiring informed consent, and proposed that we place dental amalgams in Class III because there is a lack of evidence to support safety. Again, getting back to this concept of affirmative demonstration of safety. And estimating the amount of mercury -- external mercury measurements should be used and taken into account such things as heating and brushing. Urinary mercury excretion studies are weak for assessing mercury. And suggested that young males are more sensitive to mercury than females.

Dr. Richardson's presentation pointed out something quite different in that urinary mercury levels are perhaps a valid endpoint for

population studies of amalgam. And that a detailed dose response study is needed. Regardless of which reference exposure level that the FDA chooses, the majority of the adult population will exceed that value based on what Dr. Richardson said.

There was an Open Public Hearing and there was a lot of things said in that Open Public Hearing, some of them reinforcing what was said in the petitions. I guess I would like to point also to what Dr. White mentioned about the very personal stories of tragedy that were attributed to mercury exposure from amalgam, I wanted to acknowledge those, as well.

We heard from the homework assignments. Dr. Ginsberg talked about uncertainty factors that should be between 100 to 300. Existing reference concentrations are unlikely to account for perinatal vulnerabilities. Difficult to find a threshold value across diverse populations. And the RfC should be re-evaluated. I need to move along.

We also heard some methods offered from Dr. Yokel and Dr. Farland pointed out that RfC is useful as a regulatory tool for populations and also put out that any uncertainty factors should have a clear explanation provided and default values may not be appropriate.

Dr. Martin's presentation discussed the Casa Pia study and addressed perceived concerns and any considerations of amalgams should account for gender.

Dr. Jean Harry from NIH also summarized possible paths for future

research. She pointed to examples of issues to consider, points of comparison, biomarkers of exposure, human clinical studies and cumulative uncertainty factors.

And seeing as I'm coming up on 30 seconds, I will just say that today were going go transition to discussing the science. We have questions about amalgam, we've put them out there. This is not a voting Panel. I just want to point that out. We are not voting on anything.

I would like to keep this discussion to the science, avoid any discussion of regulation. None of our questions deal with regulations. If you have questions about regulations to help you move towards the science we would be glad to answer them.

I want to thank everybody for being here. Hopefully we can to get this very important problem. Thank you.

DR. JEFFCOAT: Thank you very much for that succinct and clear, which is not always the same thing, and thank you for bringing them together, wrap up of what we heard. And I really do want to stress we did really hear some very compelling stories of problems that people have had, but now we are going to need to see what science really exists and where are there are gaps.

Before we got to the questions, and we do have a number of questions to get to. The Panel has the questions and we have 10 questions. And if we just do that evenly we would need to get to them all in 30 minutes per question.

Dr. Griffin and Dr. Dourson have put together a summary of how amalgam works and the terminology because we all come from different backgrounds, meaning the Panel, and for those in the public who are listening, many of those people come from different backgrounds, many -- we've heard from many of them about what they are. So it will be very helpful and we appreciate -- I want to express my appreciation for you doing this last night in your rooms. Thank you.

DR. DOURSON: Okay. Top of the morning to all, it's good to be here and to talk a little bit about reference concentration. We have 10 slides, 8 of them on reference concentration, sort of, to give you an idea -- it's a well-worked area of science -- and then 2 slides on mixtures. And both Susan and I have worked a number of years in this area, so let's get into it.

First of all the focus of this 10 slides is on the National Academy of Sciences Paradigm of several years go. It's sort of framed the risk assessment idea and what you're going to hear is really risk assessment is preventive medicine. So what we're trying to do as scientists and in this area as toxicologists is to prevent the toxicities from occurring in a preventive sense.

So we're going to talk specifically about dose response and hazard characterization or hazard assessment. And I'll defer over here to Dr. Griffin to talk about how we characterize risk.

DR. GRIFFIN: Okay. There's both a qualitative and a quantitative aspect to this. When we begin, we collect all the literature from animal and

human studies on toxicity assessments of a chemical. With EPA it's predominantly animal studies. We don't often have that much human data. And from those body of literature what we try to do is try to identify the affect which -- the adverse affect which is consistently occurring at the lowest dose levels. And it's this qualitative assessment which we identify what's called the critical effect.

DR. DOURSON: Which was defined here as, by EPA, as the first adverse effect where it's known an immediate precursor as dose occurs. So a chemical like mercury or a chemical like a pesticide may have a whole spectrum of effects. What the risk scientists try to do is determine the first one or its precursor; if you protect against that effect you protect against all effects. And that's sort of the concept behind the reference concentration. You're going to look for the critical effect first and then in a very simple idea let's define this --

Sure, go ahead.

DR. GRIFFIN: Okay, this is the definition, the RfC. I think you saw those yesterday with Dr. Farland. But it's an estimate with uncertainty that is protective for the most susceptible populations and it's a dose that someone can be exposed to for a lifetime without a likelihood of incurring an adverse effect.

DR. DOURSON: Right. So mechanically one way to look at this is that this is a no observed adverse effect level -- no observed adverse effect level in a sensitive population. That's synonymous with the definition of reference concentration. So as we look at this mercury database we can look for sensitive

groups of people that have been exposed, we can look for their effect levels or no effect levels and that will help guide us into our discussion about the science.

When you don't have a sensitive human population's no observed adverse effect level or low effect level, then you need uncertainty factors in order to get the reference dose. And here's the equation, RfD; RfC; no observed adverse effect level, NOAEL; lowest observed adverse effect level or benchmark dose -- that's a mathematical way to sort of get your NOAEL or LOAEL, and the divide by a uncertainty factor or modifying factor.

And I think the next is an example of -- oh, these are the uncertainty factors. Go ahead.

DR. GRIFFIN: The uncertainty factors. Okay, you know, once you've identified your critical effect from your database, whether that be renal toxicity -- toxicity, neurological toxicity, you try to then identify the lowest observable effect level or no observed effect level from those studies. Once that is done, this is what we can consider our point of departure, our critical effect level. From that we add uncertainty factors to account for five different areas of uncertainty.

The first area being variability amongst human beings. This is including differences in gender, differences in ethnicity, differences in age, differences in genotypic phenotyping. So this is for sensitive individuals.

A second area is, again, mostly EPA deals with animal data. When we're converting from animal data to a human critical effect level.

A third area would be if we only have short-term studies. Remember that the definition of the RfD or RfC is this is a dose someone can be exposed to for a lifetime. So if one only has short-term studies we use another uncertainty factor to convert to a lifetime safe dose.

A fourth one, if we only have a low-effect level that's identified as adverse, opposed to a no observed effect level.

And the fifth one is what they call a database uncertainty. But for all intents and purposes it's become synonymous with a child safety factor. And in this particular uncertainty factor what we're looking at are reproductive and developmental studies that try to define effects occurring in utero and pre and postnatally.

DR. DOURSON: Okay, so with -- when we do these uncertainty factors, back in 1958, Lehman and Fitzhugh, U.S. FDA kind of put this forward. There were the 10-fold defaults. And what we do now is we look for data first, so we're going to look for data as a first resort and if we don't have data we're going to go to a 10-fold default. Sometimes we use intermediate factors.

One of the misnomers you will find is people say, well, you know, humans are more variable than 10-fold so why do you only use 10-fold? But what happens is we use 10-fold on the no observed effect level of a human group. So it's a group of individuals, we're already at the end of the low end of the dose response curve because it's the no observed effect level; it's not up on the dose scale. We're going to take 10 from there. So when you use 10-fold

there you're actually accounting for more variability in the human population than just 10-fold in your own mind. So it's actually much higher, maybe even 100 or 1,000-fold.

So we're going to give you an example now. And this is --

DR. GRIFFIN: Actually, I let you do this example.

DR. DOURSON: Okay. So this example is off the U.S. EPA's Integrated Risk Information System, again a system that's open to the public and this is fluoride. And what you're going to see here -- actually, this is off the ToxNet, the National Library of Medicine's ToxNet and the database is the ITER, International Toxicity Estimates for Risk.

What this is doing is summarizing the safe dose for fluoride with three different organizations: the Agency for Toxic Substances and Disease Registry, Health Canada, and the U.S. EPA. And what I would like to point out here is uncertainty factor. In the case of ATSDR, the uncertainty factor is a threefold and there's a way to describe how they justify it. But what's -- the point here is in Health Canada and U.S. EPA, they've used a one-fold uncertainty factor. And what this means is that in both cases Health Canada and U.S. EPA, they have got human data in sensitive humans that defines in their judgment the no observed effect level. And so when they have a sensitive human no observed effect level, and these humans happen to be children, the uncertainty factor is 1, in effect, you have the reference dose in this case or reference concentration if it was inhalation.

So that is sort of the eight slides about reference concentration. You'll probably have a few questions. But we also wanted to give you two more slides, and this is on chemical -- oh, pardon me, I guess three more slides. Here, this just saying that the reference concentration, reference dose, account for sensitive populations, by definition they do.

DR. GRIFFIN: So when you're asked later on to consider the effects of a chemical on, again, exposure in utero, prenatal, postnatal, exposure to sensitive individuals, we hope this gives you an appreciation of what the reference concentration actually can envelope.

DR. DOURSON: Okay. So -- thank you for that addition.

So now we have just two slides on mixtures. This came up yesterday because some people say, hey, we're exposed to more than just one chemical. Well, indeed we are. And so EPA and others have developed a guideline on mixtures and we have two slides and I'm going to let Dr. Griffin step through because she deals with this routinely.

DR. GRIFFIN: Okay. Well, typically when we're dealing with multiple contaminants, and we never really deal with one, it's always multiple contaminants and we have to consider the effects from each of these and we have to add up all the different risks from all the different contaminants. So it's the total cumulative risk that's being considered; it's not just risk from an individual contaminant.

DR. DOURSON: Right. So therefore, if you have a situation where

you have a well-defined mixture of chemicals you use that data first. You use the data on the mixture if you've got it. If you don't have that particular mixture of chemicals data, you use a sufficiently similar mixture.

A good example of that is polychlorinated biphenyls in fish. We have good information on laboratory mixtures of PCBs. We can do reference doses on those. But when it goes into the fish the mixture changes. Is it sufficiently similar or not, that's the question.

And then if you don't have either of those you go to a risk assessment based on components and that's the individual chemical assessment and then the addition various ways to add. And EPA's been doing this for a number of years, a number of guidelines. They are not the only agency that does this. In fact, they're not the only organization that does it. Similar throughout the world different organizations use methods like this to address multiple chemical exposures.

So at this point if there are questions we would be happy to try to answer them but then otherwise I'll defer to our chair, Dr. Jeffcoat.

DR. JEFFCOAT: Yeah, questions from the Panel. Yes?

DR. KOTAGAL: Suresh Kotagal. You know, with regard to the issue of no observed adverse effect, you know, I guess we are using tools like psychometric assessments, Wechsler Adult Intelligent Scale, et cetera, motor skills, but you know, these are tests that were developed 30 years ago, 40 -- 35 years ago. Are we -- have we used current state-of-the-art techniques to

measure adverse effects, such as functional MRI, such as magnetic resonance spectroscopy or proteomics for that matter?

So I -- you know, my question is why are we depending upon age old measures of adverse effect?

DR. GRIFFIN: When EPA is developing these reference concentrations and reference doses, we work off the available literature that's been published and peer reviewed. So I guess the question would be up to the researchers that are doing these studies, as opposed to -- we evaluate what is out there in the open literature.

DR. DOURSON: Right. And just a slight addition. If -- we're generalists; we're not clinicians. So if we get to a toxicity or an effect of which we're unaware of the significance, we're going to go to the clinicians and ask them what does this mean. This is the tie-in to the medical community that we often do because we need to.

DR. ANUSAVICE: I think, if I can say something, I mean, I think a lot of these designs are driven by what's been done with lead and what's been done with methylmercury, because if you look at the design -- designs of these studies they're very much like what was done on the Seychelles Islands, what was done in the Faroe Islands with methylmercury. It's a lot like a lot of the lead studies that were done. So I think -- you know, I think that, you know, these are traditional tests that have been used and proven to be sensitive for other compounds for development exposures.

Now, I know for a fact that some -- the folks in the Seychelles and the Faroe Islands are starting to do imaging studies, as well as these functional studies. But that's very costly and I don't know how far along that is. I haven't seen anything in the literature so far based on their image results. I think there's one or two papers that may be out. But I think for the most part these studies are traditional. They've been sensitive to other compounds, so there is, I think, a reason to start with them.

DR. ANUSAVICE: Thank you, I am taking over temporarily as chair. Our chair became ill, so I will try to do the best I can in following through with the protocol. Thank you.

DR. TINANOFF: I'm a practicing dentist, not a toxicologist so I had to -- please excuse me if I'm totally off base here. And so I just tried to come at it from just a quick search this morning on other agents that possibly could have an RfC to see how mercury would fit in with these other ones. And so I just -- from the periodic table I just picked out a few: lead cadmium, and tin, palladium, and some of those aren't appropriate. But one that came up, what I looked at, that had an -- well, mercury has an RfC, lead has an RfC, and cadmium has an RfC.

What it said for lead was that the EPA finds it inappropriate to have an RfC because it's so low that it's without a threshold. So I'm confused here about toxicity of lead versus toxicity of mercury and how would they relate with regard to RfCs?

DR. GRIFFIN: You know, you have picked the one chemical for which EPA has developed a different method for assessing risk.

DR. TINANOFF: Sorry.

DR. GRIFFIN: You found the one. But EPA follows the Centers for Disease Control guidelines of 10 micrograms per deciliter as a blood lead level of concern. And what they have done is they have employed a pharmacokinetic type model to estimate in an internal or absorbed dose, and then compare that to the Centers for Disease Control level of concern.

DR. DOURSON: So in that particular case the threshold for concern is 10 micrograms per deciliter. Lead is not given a reference concentration; it operates in a different way, the assessment is. And if you had sufficient data you could do that for other chemicals, as well. And other chemicals have done more exacting assessments, other than just reference concentration.

DR. TINANOFF: So the level of concern is more accurate or less accurate or it's completely different?

DR. DOURSON: No, in this particular --

DR. GRIFFIN: It's -- oh, I'm sorry. The level of concern is not more or less accurate, it's simply based on neurological effects in young children as a sensitive subpopulation.

DR. DOURSON: And so again, the concept is for the reference concentration there is a population threshold. You've estimated what you think

is -- what you think is a sub-threshold dose but there's imprecision in the estimate, it's likely to be without risk of deleterious effects for sensitive individuals but there is some qualifications there. It's more qualitative than the more exact physiologically based model that lead's based on.

DR. TINANOFF: But it's also based on the weight of evidence from the studies, right, that there isn't a threshold? I mean, that's --

DR. DOURSON: For which chemical; for lead?

DR. TINANOFF: For lead.

DR. DOURSON: I think in the toxicology community that would be argued. But what's not argued is that there is a 10-micrograms per deciliter action level. And whether there is the threshold at lower doses or not would be argued amongst the toxicologists.

DR. TINANOFF: But the lack of EPA providing and RfD or an RfC, in my understanding, it's based on the weight of evidence that would indicate that there isn't one?

DR. DOURSON: Well, I think it's just based on a better way to approach it with a different model. It integrates --

DR. GRIFFIN: One way you could perhaps look at it is --

DR. ANUSAVICE: Excuse me in the interest of time, we are 30 minutes behind schedule, so we have one more comment and then we have to open it up for the FDA questions.

DR. ASCHNER: So I have a very -- I'm a toxicologist but I don't do

risk assessment, so maybe you can clarify it for me. Let's assume that we have three different metals for which we don't have any information on children, for example, what would lead you to assign values of 3 versus 10? What are some of the criteria that you would use to assign a 3 or a 10 or a 100, whatever number you wish to use?

DR. GRIFFIN: That's a very good question. I'm glad you asked it. For the database uncertainty factor or the child safety factor what we do is we look at reproductive and developmental studies in the database.

There are EPA guidelines as to how those studies should be conducted. So if we have single-generation and two generation reproductive studies and we have a developmental study conducted according to guidelines, we consider that an uncertainty factor of 1. We do not need to add an extra uncertainty factor.

If one of those studies is missing, for example, a two-generation reproductive study, often times we use an uncertainty factor of 3. We just did that for a chemical file on benzoate pyrene.

DR. ASCHNER: Do you ever assign a 10?

DR. GRIFFIN: If all that data is missing, you have no reproductive and no developmental studies we'll assign a factor of 10.

DR. ASCHNER: And do we have those data for mercury?

DR. GRIFFIN: Yes, we do.

DR. ASCHNER: Inorganic?

DR. GRIFFIN: Elemental vapor. Mercury vapor.

DR. CLAUDIO: I know there are other questions. In the interest of time remember that you can ask the Panel leads, Dr. Griffin or Dr. Dourson, if you want to clarify something before discussing. So we'll continue now with the questions and if you have any other questions from them you can say, "Can you please clarify this?" and then continue the discussion, okay?

DR. DOURSON: Thank you.

DR. ANUSAVICE: Okay, thank you very much for that presentation.

At this time we would like to focus our discussion on the FDA questions. Copies of the questions are in your folders. And Panel members, in order to help the transcriber identify who's speaking, please be sure to identify yourself each and every time you speak. Please show the first question.

MR. ADJODHA: This is Michael Adjodha. I'm an engineer in the Dental Devices Branch of FDA.

DR. ANUSAVICE: Speak a little closer to the microphone.

MR. ADJODHA: Yes, sir. Certainly.

FDA seeks input from the Panel on three sets of scientific questions. First set of questions concerns a level of exposure to mercury that amalgam bearers receive from dental amalgams. The second set of questions concerns how the reference exposure level for elemental mercury or the level considered protective, assuming chronic exposure of the general population and

vulnerable subpopulations should determined. The third set of questions concerns clinical studies of exposure to dental amalgam. The final set of questions -- a final question concerns how to weigh risk assessment information and clinical information in FDA's regulatory approach.

Your answers to these questions will assist FDA in evaluating it's current regulatory approach and whether changes to that approach are warranted.

The first question: As you heard, petitioners argue that FDA underestimated level of exposure to mercury from dental amalgam and failed to adequately consider differences among different age groups that could affect absorbed dose.

In its final rule, FDA used estimates for absorbed dose of inhaled mercury vapor from an average number of fillings of 1 to 5 micrograms per day. The petitioner's relying on the 1991 and 2003 WHO reports on elemental mercury and inorganic mercury compounds state that the absorbed dose can range from 3 to 17 and 1 to 22 micrograms per day respectfully.

I would like to modify Question 1(a) a little bit and remove the word "different." I'll read the question as follows: Assess the strengths and weaknesses of the data supporting the exposure assessments from HHS and WHO reports. And the reason is -- the reason is because the HHS and WHO reports both report that the absorbed dose is between 1 and 22 micrograms per day.

Part (b) is: Based on these reports, what is the best estimate of the range of daily absorbed dose of mercury vapor from dental amalgam in the U.S. population?

DR. JEFFCOAT: Please excuse me. We are open for discussion on this first question. Panel -- ah, there we go. I'm going to put my glasses on, Dr. O'Brien, so I can see you.

DR. O'BRIEN: That's a good strategy.

DR. JEFFCOAT: Thank you. Yes.

DR. O'BRIEN: I have done research and published in -- several years ago in *Dental Materials Journal* and it's centered on the release of vapor during setting. And this goes back to a lot -- old literature, Frykholm, that's been discussed. And we found, this was all in vitro, that when you put a sample of amalgam in a bottle, that the -- for 5 days, the amount was extraordinary. And then after that it leveled off. And I don't think that can be -- this data doesn't take that into consideration. And that is clinically supported by urine analysis, that the most vapor is released during the first 5 days, and it's many times the -- after that the daily release of amalgam.

And I think this is supported in the literature and many publications have supported this, that clinically it's the most risky level. And it's -- it lasts about a week and then it subsides, and it's due to the fact that the reaction that takes place between mercury and the alloy, which is essentially AG_3SN, which is three parts of silver to one part of tin, but that reaction does not

-- it takes days to complete so that initially the restoration is really a mixture of AG_3SN and mercury. And these estimates don't take that into account.

And other data has shown that removing an amalgam, you just by -- unless it's done very carefully, as mentioned here by many dentists that do that, that the heating of the amalgam during removal by a burr releases another burst and you essentially get a repeat of the spike in mercury release for about a week, you see. And these daily doses that are mentioned, I really question this because the population has a continual average normal mercury level that doesn't seem to be harmful from dietary sources, so that if we don't take this spike into account we're missing the most clinically relevant increase in the mercury level: putting it in and taking it out. And so that's my main objection to this discussion.

DR. JEFFCOAT: Yes, Dr. Ismail.

DR. ISMAIL: I went back to the study that's mentioned yesterday, the Y study and it's the -- the first author is Eshetuvi (ph.) and it's from Rochester, New York about methyl versus inorganic mercury. And the conclusion from that is interesting, which is not addressed in setting the standards, and I'll read the results: Statistical analysis using linear mixed effects models show that methylmercury dose was the primary determinant of both organic and inorganic brain mercury levels.

So these standards do not address this effect modification on the interaction between methylmercury and mercury -- inorganic mercury. And I

think if we move forward we need to consider the total mercury intake.

DR. JEFFCOAT: Yes.

MS. RUE: Karen Rue, Consumer Representative. I wanted to ask, can I make a general statement from a consumer representative --

DR. JEFFCOAT: Certainly, you may.

MS. RUE: -- as we start discussion?

DR. JEFFCOAT: Of course. That's what you're here for.

MS. RUE: I just wanted to state historically we've been here before. We've seen rediscussions with aspirin in the pediatric population as Rye's Syndrome was produced. Antidepressant issues as it related to suicides in adolescents, we had a relook at that. Silver nitrate eye prophylaxis for newborns, and then a non-drug, but also we looked at the sensitive populations in alcohol and fetal alcohol syndrome. So I think we've been here before and we really need to readdress and look at sensitive populations as we have done in the past. Thank you.

DR. JEFFCOAT: Okay. Dr. Bates.

DR. BATES: Thank you. Just some comments on the -- exactly the question as it is. The U.S. PHS report is looking at the U.S., whereas the WHO is actually looking globally. So the U.S. report, which I read it through fairly detailed, it seems more specific to the United States, so that's I suspect is the reason for the difference between the two.

Another point though is that from everything we've been hearing,

the placement of amalgam fillings has been decreasing over time, so it's likely that the U.S. PHS report is out of date anyway, and so the values presented here are probably wrong, or out of date, at least. And I'm just wondering how useful it is given the shifting -- the decreasing placement of amalgam fillings to actually try and specify something like this because it's soon going to be out of date. And I'm wondering whether it would be more useful to come up with a value for -- an estimate value for a single amalgam surface?

And perhaps specifically it might be useful to have a separate value for an occlusal surface because they appear to be the ones that generate the most mercury that's absorbed.

DR. JEFFCOAT: Okay. So you're not talking about -- I just want to make sure I understand so we can capture it. So when -- you're saying not the total load in the mouth but to set standards based on what a single occlusal surface --

DR. BATES: So it's not really a standard, it's a -- you know, it's a scientific --

DR. JEFFCOAT: Okay.

DR. BATES: -- estimation of the amount being released. But it seems to me --

DR. JEFFCOAT: And you have to multiply it?

DR. BATES: Yes.

DR. JEFFCOAT: Okay.

DR. BATES: So then you would know how much was in a person's mouth.

DR. JEFFCOAT: That's --

DR. BATES: And you could take that value and say well at the present time, you know, the range of amalgam fillings in people's mouths in the United States is such and such, therefore we multiple it out and we come up with a range.

But it -- I think it would be better, more useful, I think, to come up with a single value or maybe two values, including one specifically for occlusal surfaces.

DR. JEFFCOAT: Dr. Griffin.

DR. GRIFFIN: The only study that I could clearly understand how they arrived at the estimates was Dr. Richardson's work in which he did a really good job with the Monte Carlo analysis. But all of this, I think, raises questions that need to be addressed.

You know, one question, for example, are we just dealing with the 50th percentile or average population or are we going to deal with the full distribution of the population?

A second question would be, I think you also just raised this earlier, Dr. Richardson depended on the estimates of Skare and Engqvist, in which he used the same release rate of mercury from teeth for toddlers, children and adults. Is that appropriate or is there going to be an age-specific release

rate?

I think it might have been helpful to me if perhaps FDA had, sort of, prepared ahead of time the different estimates that are out there and the assumptions that went into the different estimates. I think that would have allowed me to make a more objective evaluation of what would be an appropriate range.

DR. JEFFCOAT: Okay. Yes.

DR. WHITE: Just from the dental materials side when I look at the values trying to answer the question, I agree with Dr. O'Brien regarding the additional -- initial dose and the dose at removal. But after that this -- we've seen such wide variability and the chronic exposure that I, as a dental material scientist, have a hard time believing anything over 10 micrograms per day. Because if you do 10 micrograms per day and you take an average amalgam restoration, the capsules are about 600 milligrams, of which half is 300 milligrams, and you take that and take, say, 20 micrograms per day as a number. You divide it by the number of days and the number of years and pretty soon half of that amount -- half of that mercury is gone after about 25 years and all of it's gone by about 50 years.

My clinical experience is that these restorations are not falling out after 50 years or even 25 years. So from a materials perspective, if you're losing that much mercury day after day, the restoration's going to fail mechanically some other way, and frankly I don't see it. So I use that, just clinical experience,

as a threshold to say it can't be above 10 micrograms per day, it has to be something lower than that for the chronic dose.

DR. DOURSON: Real quick question. Is that per restoration or is that just generally for a whole mouth full of them?

DR. WHITE: That's a good question. It's just -- it really doesn't matter. I've seen people with one restoration that -- lots of people with one restoration that's 50 years old, but it is for a whole mouthful. So you would have to prorate it.

I still don't see the material degradation after 10% or 20% material loss; I just don't see it. So I have a hard time with that number.

DR. DOURSON: Thank you.

DR. JEFFCOAT: Okay, one last thing and then I want to try, between myself and Dr. Anusavice, who was kind enough to take the chair, to stop --

DR. FLEMING: Thank you, this I Mike Fleming. I have one comment and then I would like to ask the FDA one question about their 1 to 5 microgram dose.

I would echo Dr. O'Brien's concern about installation and removal being spiked, but we have multiple spikes throughout the service life or life cycle of an amalgam, which would be during the course of eating, chewing, other stresses on the dentition that we all are aware of as clinicians.

And then finally, most offices usually see their patients on recall

visits at 3 months, 4 months, 6 months and every time that prophy cup touches that amalgam, there is a massive release of mercury from these restorations and that spikes and may very well last another week.

And so therefore I don't think that this dose that you're seeing here -- I think you sort of have to look at this as just an average. I do not think that even after 40 years you would lose 20% of the mercury. If you think about 300 milligrams of mercury being in an average restoration and 10 micrograms per day, you have to calculate how many years it would take for that.

But still we are dealing with a microgram range that's of interest of to me. I wanted to ask FDA, you relied, am I not mistaken, on the '93 U.S. Public Health Report for your 1 to 5 microgram range? I believe that you did; is that correct?

DR. GOERING: Yeah. I'm Peter Goering. I'm a toxicologist at the Center for Devices and Radiological Health. Yes, we did rely on the --

DR. FLEMING: That study? Was that blood-derived? As I read the statement that talks about 1 to 5 micrograms, in the sentence just prior to that: Measurements of mercury in blood amongst subjects with and without amalgam restorations, in subjects before and after amalgam was removed, provide the best estimates of daily intake from amalgam dental restorations. These values are in the range of 1 to 5 micrograms.

So is my assumption correct that this was a blood-derived number?

DR. GOERING: Could you tell me if you're reading from the '93 report? Is that --

DR. FLEMING: I believe that I am. I had -- it's under Conclusions. 1993 USPHS. If I'm looking --

DR. GOERING: My --

DR. FLEMING: And the language is almost literally duplicated in the final rules language.

DR. GOERING: I do not think they're -- the 1 to 5 microgram per day estimate is related to a blood mercury -- blood mercury assessments.

These studies of mercury release were published primarily in the 1980s. There may have been one or two in the early '90s. This multi-agency panel in '93 reviewed those exposure assessments and I believe some of the studies were also used by Dr. Richardson, who spoke yesterday, and they appear in his recent report, and the range is similar, 1 to 20; 2 was the absorbed range of estimates that were absorbed. Those studies each had an average and a range associated with them.

If you look at the 14 or dozen, 15 studies the average of those averages is about 5 micrograms. And so I think that's basically where this -- the risk assessment done in '93 derived that average estimate for the entire population. I believe it was not --

DR. JEFFCOAT: Dr. Anusavice?

DR. GOERING: -- was not stratified.

DR. ANUSAVICE: Yeah, Ken Anusavice. If I could amplify on that? And one of the original studies was done by Anders Berglund in Sweden where he measured mercury vapor release from the patients who had -- these are healthy patients, ages 24 to 40, who had on the average 13 occlusal surfaces and total numbers ranging from 9 to 18. I just jotted these down the other day for my reference. And they had a mean of 27 total surfaces ranging from 13 to 48. And five controls without amalgam.

And Anders had these subjects hospitalized so we could watch them for 24 consecutive hours. Had them brush, take food, do whatever they normally did in the daily activity, except for prophies -- I don't think prophies were part of that analysis. And they found levels that were confirmed by others after that. Berglund's value is 1.7 micrograms per day over 24 hours. Then he did a collaborative study with Mackert, who was here and you heard from earlier, who both concluded the dose would be 1.8 micrograms of mercury per 24-hour period.

And then there are other values. So those studies were done in 1990, 1987; you're right on the time period. And then Langworth had a published value of 3.0 micrograms per day. And then finally Snapp et al. in 1988, 1.3 micrograms per day.

So we're hearing ranges of values and I think it would behoove to really be careful about what the conditions were of the study. So I refer primarily to Berglund's initial study because I know, and I've spoken to him in the

past, about how carefully that was controlled. And then Mackert gave a presentation today to support the 1 to 3 microgram range. So he's one of the experts in vapor inhalation effects and measurements. So I would support the 1 to 3 range for sure.

DR. JEFFCOAT: Okay. I think we need to make sure -- we've got a number of other questions to get to. If we don't get to an answer we can leave it and come back to it, all right? I think you have discussed the strengths and weaknesses of the existing data. I don't hear good consensus.

And Ken, please correct me -- also correct me, anybody, on what the range actually is. Am I wrong? Yes.

DR. DOURSON: Mike Dourson here. I just wanted to ask a question to my colleagues. The numbers that I'm hearing I believe are the averages?

DR. JEFFCOAT: Yes.

DR. DOURSON: And Dr. Griffin, based on what Dr. Richardson said yesterday is there's another way to look at this, it's whole distribution of intakes, a distribution range, and of course both of these things might be right. The averages might be 1 to 3 and the distribution might be 1 to 22. The question is has FDA tried to replicate the Richardson work or do you espouse the kind of distributions of exposures that might be -- that you might be able to put together with these data?

DR. GOERING: We have not stratified the exposures in the

population per Dr. Richardson. And it is something that we'll take a look at.

DR. DOURSON: Thank you.

DR. BURBACHER: Just a as a comment?

DR. JEFFCOAT: Okay, yes. Okay, quickly so we can --

DR. BURBACHER: I was going to bring that up, as well. But if you just look at the consistencies and the remarks related to this, the 2006 panel, their comments were the same, that this distribution should be done and not relying on average.

DR. JEFFCOAT: Okay.

DR. BURBACHER: And then I think at least two of the three folks that did their homework, you know, said that that had to be case, as well. So I think, you know, I think it's an important message that's, you know, come across a few times over the last few years.

DR. JEFFCOAT: Can we live with that as a committee?

Dr. Griffin?

DR. GRIFFIN: I'll be real quick.

DR. JEFFCOAT: Yeah.

DR. GRIFFIN: The number of amalgam surfaces appears to be an influential variable in the equations. And I think today we heard that there seems to be a discrepancy or big difference between what was in the NHANES data and what the gentleman from the insurance company reported. So I think that's one variable that really ought to be explores since it has so much impact.

DR. JEFFCOAT: Yes?

DR. ASCHNER: I would like to amplify and also ask the FDA to look possibly at the potential effect or potential exposure that is associated with the kinetics, as was mentioned, so we get a better understanding of exposures at various periods, not just an average exposure, because one high exposure might be much worse then a continued exposure for 20 years.

DR. JEFFCOAT: Okay, the very last one. We're going to go on to the next question.

DR. DOURSON: Okay, and just a very quick addition to that. There are things like acute exposure guidelines levels, the EGLs, that attempt to do 8-hour spike exposures and how to deal with them. And you know, for inorganic -- I'm sorry, for elemental mercury it's 0.33 milligrams per meter cube. So we have targets that we can hit on that, as you probably well know. Sorry.

DR. JEFFCOAT: Okay. So we do not have a number but we have sort of a strategy to go forward to get a series of numbers for different populations, okay.

Ken, is that -- I don't want to speak in case I haven't --

DR. ANUSAVICE: I would rather not present my opinions, but --

DR. JEFFCOAT: Oh, no, I mean what happened while I was --

DR. ANUSAVICE: -- but I'm hearing variables here --

DR. JEFFCOAT: -- while you had the chair.

DR. ANUSAVICE: -- and others that were mentioned yesterday,

confounders that we haven't even brought into this discussion.

DR. JEFFCOAT: Right.

DR. ANUSAVICE: For example, alcohol consumption, tobacco use. We know that alcohol decreases mercury release in blood and smoking increases it and so forth. If you live near a fossil fuel plant what does that do to the contribution?

DR. JEFFCOAT: Right.

DR. ANUSAVICE: And where is this being measured and so forth. So I think there are a lot of confounders that have to be somehow mentioned in this whole scenario, as well.

DR. JEFFCOAT: Okay. Question Number 1, exposure to mercury from dental amalgam.

Question 2, under it: In the final rule FDA considered differences in respiratory rates and volumes between children and adults for estimating daily doses of mercury vapor from dental amalgam.

Some of these things we may have covered in the way our -- we have consensus of a way to go. Okay, I've got it written down. Yeah, we -- the consensus is that we do not have individual guidelines at this point and FDA has not stratified the exposures that Richardson reported, which were basically based on averages, but we need to go forward and get the exposures, for example, children, for example, different groups.

Okay, Mr. Watson, is that adequate?

MR. WATSON: It looks like according to my staff, yes, it is.

DR. JEFFCOAT: Okay. Now we'll go to the second question. Okay. Oh, the FDA staff reads it. I'm sorry, I stepped on your -- stepped on your toes, I'm sorry.

MR. ADJODHA: It's okay.

DR. JEFFCOAT: You can go ahead and required Question 2.

MR. ADJODHA: This is Michael Adjodha, FDA.

In the final rule, FDA considered differences in respiratory rates and volumes between children and adults for estimating the daily dose of mercury exposure from dental amalgam. FDA did not incorporate body weight in these estimates. FDA also did not consider differences in the number and size of fillings and surfaces between children and adults. The petitioner's state that body weight and other factors should have been considered when making comparisons between children and adults.

How should the following age-related parameters factor into FDA's analysis: (a) inhalation physiology parameters; (b) body weight or body mass; (c) number of amalgam surfaces and filling size; and (d) are there any other specific age-related physiologic, genetic, pharmacokinetic differences of mercury vapor exposure that should be considered in the risk assessment?

DR. JEFFCOAT: Okay. Yes?

MS. RUE: Obviously pregnant women need to be addressed, but also please consider the fact that there's some youth that are larger than some

adults with just their developmental systems, their neurological systems are still fully not developed, so body weight and mass needs to be taken in consideration with developmental stage, also.

DR. JEFFCOAT: Yes, I'm sorry.

DR. ZELIKOFF: May I address the inhalation physiology parameters first?

DR. JEFFCOAT: Yes, go right ahead. I'm sorry, I'm just writing down what she said.

DR. ZELIKOFF: That's okay, he already said yes.

I think that the inhalation physiology parameters between children and adults are like comparing apples and organs. There are so many differences in the physiology and structure of the lung in a child versus an adult. And many of these alterations include things like the size and number of the alveoli, which increase dramatically and don't reach the full potential until young adulthood. The fact that the lung recoils different in children and adults, which is less of recoil than the adult because there is reduced collagen. There are structural changes in the chest wall. There is less collateral lung exchange. There's increased airway resistance in children. There's a real host of differences in the physiology of the lung in children.

This could -- these differences really could make a difference in terms of the vulnerability to toxic insult with mercury because children and -- young children and even a little older children are kind of working on a

diminished capacity to begin with, and so I think that this is an incredibility important parameter that has to be considered when talking about perinatal, neonatal and children in general.

DR. JEFFCOAT: May I just ask a question? Is age sufficient or do you need to actually measure volumes --

DR. ZELIKOFF: Yeah.

DR. JEFFCOAT: -- in individuals? I mean --

DR. ZELIKOFF: That's a very good point. That takes into account --

DR. JEFFCOAT: In your opinion, expert opinion.

DR. ZELIKOFF: I think that's an excellent point and that is that there are many individuals, adult individuals who have diminished volume, diminished capacity in that regard, such as those with chronic obstructive pulmonary disease or emphysema or chronic bronchitis. And I think that all of those parameters have to be considered, not just age.

DR. JEFFCOAT: But you might do that by history; is that what you're saying?

DR. ZELIKOFF: You can do that by history, doctor diagnoses, yes.

DR. JEFFCOAT: Okay.

DR. ZELIKOFF: Easily measured by forced excretory -- measured by force volume, FEB1; clearly a validated excellent way of diagnosing many of those lung diseases.

DR. JEFFCOAT: Thank you. Dr. Tinanoff?

DR. TINANOFF: As I read through these documents, over and over it states that there's no data for children under age 6 and I don't think we can extrapolate from adults to children, and especially to infants because there's quite -- as we just heard about the lung capacity and differences of physiology with regard to the lungs, the differences with regard to blood/brain barrier and not many other factors. So in my opinion we just don't know and we can't extrapolate until we get real data for children under age 6.

DR. JEFFCOAT: Dr. Tinanoff, can you also comment for the entire Panel about the differences between adult -- what people call adult teeth or permanent teeth and the deciduous teeth, because there would be some differences, I would think, as not a pediatric dentist.

DR. TINANOFF: Right. I think the difference is, like what Dr. Bates mentioned, would be looking at it per tooth and there would be some differences per tooth between an adult tooth and a child's tooth.

First of all, a child's tooth is much smaller but the surface area of the restoration may be larger. So we need some data with regard to what would those -- how much amalgam would be placed in one tooth in a child, in a child's molar, versus an adult. And I don't know if there's -- that data exists right now. But I strongly suggest that we look at this at a per tooth level, both for the adult and for the child.

DR. JEFFCOAT: Thank you. Yes?

DR. STANFORD: To add to that, I think one of the things that

people have been talking about, I think surface area seems to be a critical factor on these and not surfaces or number of restorations; it's really the surface area that's going to be a critical feature to look at.

The other one we've already touched on which is the pharamcodynamics, which is the time from placement, especially in the younger child.

But one that -- issue we have not even - - no one seems to have mentioned yet is the impact of the salivary proteome, the biofilm, and the fact of the microbial population and its impact on the surfaces, as well as salivary flows, changes in salivary composition as age; all of these components are also part of this formula and it's not an easy one to put together.

DR. JEFFCOAT: Do we have any evidence that that matters or you're just saying that we need to look? I just want to --

DR. STANFORD: Well, I can only speak for some of the congenitally affected populations I deal with --

DR. JEFFCOAT: Um-hum.

DR. STANFORD: -- and that is the salivary proteome and the salivary composition is extremely different than what you find in the common garden variety child that you -- might come into a practice.

DR. JEFFCOAT: Okay. Yes, Dr. Aschner, I'm sorry. I promised you a little while ago.

DR. ASCHNER: Well, it's okay. Thank you. I just wanted to

reinforce the fact that age is very important, I think, especially, although not very common, I understand, if amalgam is placed in a pregnant woman or very early in the neonatal life. Because many of the systems that are responsible for mercury excretion actually don't develop until postnatal change. So again, in addition to the three issues that are listed here, I think one of them that maybe should be added is age.

DR. JEFFCOAT: Yes.

DR. BURBACHER: I actually think pregnancy and the fetal exposure, you know, should be really given a lot of thought because, I mean, there are -- for methylmercury there are changes in the half-life of mercury during pregnancy; you know, who knows what it is for mercury vapor. Do we know much about, you know, how the fetus is exposed during pregnancy? How the distribution in the fetal brain -- how -- what the excretion pattern is. I mean, all that we don't know anything about. So in terms of what's the exposure and body burden kinds of issues with fetal exposure we just don't know anything at this point.

DR. JEFFCOAT: Mr. Watson?

MR. WATSON: Hello. I just wanted to make sure that the Panel is -- if you could -- what would be very helpful to us, because what we're going to have to do is take this information and go back and work with it. We're not able to generate a lot of this information.

DR. JEFFCOAT: Right.

MR. WATSON: I want to make sure that the questions that you're -- information that you're putting out there can -- maybe you can help us by separating those things that you think are actually in the information that's out there and things that you think we need to look at down the road, because obviously everybody in this room wants something to happen quickly. So do we. So it would be helpful of us to know if we have to find someone to generate that information or we have it available to us.

DR. JEFFCOAT: Yes.

DR. KOTAGAL: So with regard to -- and body weight and body mass, a study using dual X-ray absorption metrics showed that the mean percentage of fat to body weight ratio is slightly higher in infants, about 27%, as compared to the mid second decade where it's about 23%. And there's a reference, Kelly et al. , PLoS ONE, 2009, volume 4, issue 9, page 7038. Number one.

Number two, since mercury is lipophillic, newborns and infants may be predisposed to greater absorption for mercury per kilogram of body weight. And as has been mentioned earlier, you know, I think we need to measure exposure based on milligram per kilogram body weight.

DR. JEFFCOAT: Okay. Dr. Griffin.

DR. GRIFFIN: I'll approach this from the risk assessment side. Risk is a function of exposure in toxicity. So on the exposure side of the house I would encourage you to use inhalation rates, body weight, et cetera that's child

specific and the exposure factors hand-picked for children.

DR. JEFFCOAT: Yeah.

DR. GRIFFIN: Oh, I'm sorry. I was saying encouraging to use inhalation rates, body weight, child-specific exposure variables on the exposure side of the equation. Also pinning down an accurate estimate on the amalgam surfaces because I think the NHANES data may or may not be representative of what's going on now. And then on the -- I doubt there's an off-the-shelf pharmacokinetic model, so.

But I think the -- on the toxicity side of the house, you're going to deal with a lot of the variables: genetic variables, for example, susceptible subpopulations. So it -- that would be on the toxicity equation.

DR. JEFFCOAT: Yeah. Okay, Norm, and then I just want to ask --

DR. TINANOFF: There is one other thing that we need to consider is that mercury may be much more harmful in a developing brain than it is in an adult brain. And so I think that's also true with lead. So that is something that I don't know if we have any numbers of about, but we need to take extra precaution here if that is the case.

DR. JEFFCOAT: Yes.

DR. DOURSON: Michael Dourson here. So this is not my area of study so I'm just going to make a comment to the rest of my colleagues. I think one reason we're interested in these answers to these questions is because the basis of the reference concentration or point of departure or uncertainty factor

is based on humans and adult human. If we instead focus on the critical effect with some of this new information, the critical effect in children, and actually use some of these children studies that are now coming to fruition, you might be able to build a safe concentration on the basis of children's data, and not obviate necessarily these questions, but if you're protecting the children because of the most sensitive human, you might be protecting the adults, as well. And these questions, while still important, step back a little bit in as far as getting them answered right away.

DR. JEFFCOAT: Okay. Let's get Dr. Aschner.

DR. ASCHNER: Yeah, I'm actually having some difficulty with the last comment. Michael Aschner.

I think, you know, even if all these data were available for children, I think plugging in a factor of 1 is not necessarily the way to go because there are many cases you might be losing 40, 50% of your neurons in the brain and if you did neurocognitive testing you wouldn't see anything, and many of these effects wouldn't be apparent until somebody's 40, 50, or 60 years of age. So I feel even uncomfortable with -- if you had those data, I'm not sure that I would be comfortable with a uncertainty factor of 1.

DR. JEFFCOAT: Dr. Ismail.

DR. ISMAIL: Yes, to answer Dr. Watson, it's very important to do a systematic review or systematic reviews looking at all the evidence that exists because I don't think we have looked at all the evidence. There are some recent

studies, the post-amalgam removal trial has some data on total integrated blood for plasma and other cells there that maybe useful to estimate it be 3 and 7.43 micrograms per day average for smaller number of restorations and a larger number of restorations 7.4. So we need to look forward and collect all the information to make a decision.

I just want to comment also on the children. In the Canadian data that we're presented, we base the estimate, and I was involved in that committee, based it on the 1940s data on flourosis. And because there was no extraneous -- there's no external source of fluoride, just the fluoride in the water, we looked at the children and we estimated backward the acceptable minimum concentration for fluorosis, and that's how the Canadian data were derived. So I do agree that we have to go to children and we have to reframe the question to look at sensitive populations.

DR. JEFFCOAT: Okay. We need to remember this question that we're discussing right now is addressing the components of error, essentially, in determining the mercury vapor from dental amalgam. We're not talking about whether it causes any problems at all, yet. Just what is the number.

Dr. Zelikoff.

DR. ZELIKOFF: As far as things stand now in terms of body weight mass, I think it's an important parameter to look at primarily maturational changes such as an increased body mass can alter the distribution, metabolic elimination of mercury. And so I think, you know, when you're looking at

increased body mass which occurs over time in terms of aging, it's something that you have to consider whether it's going to be excreted to the same rate, whether it's going to be distributed differently.

Another thing that I just wanted to bring up in terms of what people are talking about in terms of prenatal exposure, very big emergence has occurred with the fetal basis of adult disease. And in looking up some of these -- some of the roles that mercury may be playing in that I came across a number of studies, and this is for future for the FDA to look into, I came up with a number of studies in terms of methylmercury and I'm sure Dr. Burbacher can talk about this in greater detail, in which prenatal exposure to methylmercury manifested itself in later time in children, as well as adults in various neurological diseases.

And I think that one would be remiss in -- especially since methylmercury and elemental mercury may -- the toxic product may be the inorganic mercury. I think that the FDA would be remiss in not looking into whether there is any long-term delayed effects in terms of disease manifestation from prenatal exposure.

DR. JEFFCOAT: Okay. In answering Question Number 2 -- or all right, last question because I want to sort of sum up and see what --

DR. KOTAGAL: Certainly.

DR. JEFFCOAT: -- if we've got any kind of consensus.

DR. KOTAGAL: This is, you know, in response to Dr. Dourson's comment about taking from the adult values and extrapolating for children. So

some of these studies, for example the study, important study, Dr. DeRouen's study which Dr. Martin, you know, discussed yesterday, I have some concerns about that study. They used a comprehensive test of non-verbal intelligence, which is the kind of test you might use for, say, deaf children, and the scores for the United States children is -- average score is 100 and that --

DR. JEFFCOAT: Doctor, I don't mean to interrupt to --

DR. KOTAGAL: Oh, surely.

DR. JEFFCOAT: -- but can you save that till we're on a question that --

DR. KOTAGAL: No, surely. The point is that data --

DR. JEFFCOAT: -- that addresses that point?

DR. KOTAGAL: Certainly.

DR. JEFFCOAT: Okay.

DR. KOTAGAL: The point is that that data is flawed, so we can't really extrapolate from some of those current studies on to --

DR. JEFFCOAT: Okay.

DR. KOTAGAL: -- reference values for children.

DR. JEFFCOAT: Because right now we're looking at levels of mercury vapor, not whether they cause disease, okay. We're going to get to whether they cause disease. That's all. I'm not saying that you're not making a valid point, I'm just saying let's get it into the right place so Mr. Watson's team will know what to do with what we say.

DR. WHITE: Madam Chair?

DR. JEFFCOAT: Yes?

DR. WHITE: As a --

DR. JEFFCOAT: Whose where?

DR. WHITE: Sorry.

DR. JEFFCOAT: Oh, there. Thank you.

DR. WHITE: As I look at the questions we've got opinions on most everything but the genetics. I would be interested in hearing --

DR. JEFFCOAT: Right.

DR. WHITE: -- something on the genetics.

DR. JEFFCOAT: Thank you. Yeah, we've got proteomics but we don't have genetics.

DR. KOTAGAL: I could comment on the genetics part of it.

DR. JEFFCOAT: That you should, yeah.

DR. KOTAGAL: Yes, okay.

DR. JEFFCOAT: Thank you.

DR. KOTAGAL: As a clinician, as a pediatrician and pediatric neurologist, I can state that yes, there are a number of genotypes, the methylenetetrahydrofolate reductase, if we have that, that affects molination. If somebody has the ApoE4 allele, yes, that effects, is strongly predictive of cognitive development. And there have been studies in children, say, with sleep apnea. Not everybody with sleep apnea has cognitive dysfunction. There are

some who do and some who don't. Those children with sleep apnea who have the ApoE4 gene, they are must more cognitively impaired. The author on this David Gozal, G-O-Z-A-L.

So there is good data in children indicating that if there is an ApoE4 allele there is a greater risk of cognitive dysfunction. That's true for other diseases but it may very well be true in --

DR. JEFFCOAT: But do we believe that affects the amount of mercury vapor, which is the question right now?

DR. KOTAGAL: Not the vapor but the --

DR. JEFFCOAT: Yeah.

DR. KOTAGAL: -- effect of the vapor it does because I think --

DR. JEFFCOAT: The effect of the vapor. And we'll get there. We'll get there. We have a question, and I've got it written down so if you don't say it, it will get put in anyway, okay?

So if we're going to try and get a consensus in considering different respiratory rates in children and in adults and pregnant women, are we really talking about building a big model where we know about certain diseases such as COPD, asthma, perhaps, and you put that it in the model; the age of the patient, the weight or the -- better yet is the index of -- the mass index, and -- let's see, what else do I have? Age, the proteomics. I'm not sure that we have specific things we would put in the model right now.

Does anybody have specific things we would -- the pulmonary

parameters we have. Children, obviously, age we clearly need to have. Whether children -- do you believe we need to have how many deciduous teeth they still have?

DR. TINANOFF: Yes.

DR. JEFFCOAT: Or -- I mean - I'm sorry, I'm not trying to do a leading question but just asking you as the expert.

DR. TINANOFF: I don't know if we can build a model because we don't know the effects on a developing brain compared to an adult. So we have too many -- in my mind we have too many unknowns right now to be able to build the model.

DR. JEFFCOAT: We're trying to build a model in estimating the daily dose of mercury vapor, okay, that's what we're trying to measure. Yeah, I mean what I think is totally irrelevant anyway in your field, but do you agree for -- we could build a model for looking at mercury vapor? Or do you --

DR. TINANOFF: Well, we could --

DR. JEFFCOAT: Because --

DR. TINANOFF: -- add in those factors but there would still be so many -- in my mind there will still be unknowns that we can't reduce this to a number at this time for mercury vapor.

DR. JEFFCOAT: Okay.

DR. DOURSON: Could we go back to what Dr. Griffin said earlier? Can we use existing idea of U.S. EPA and others to build distribution ranges, one

for adults --

DR. JEFFCOAT: Yes, that's the --

DR. DOURSON: -- one for child? I mean, it's done --

DR. JEFFCOAT: Yes.

DR. DOURSON: -- routinely elsewhere. I'm not saying the data would support it here, but again, not the effects but the distribution of exposures?

DR. JEFFCOAT: I know everybody wants to talk about the effects so I'm trying to get us there.

DR. BURBACHER: No, I mean, to be able to do that for fetal exposure you would have to have an all completely maternal fetal model, which they do develop and there is one for methylmercury. But one of the things that I've noticed is in -- for mercury vapor, I mean, as you had mentioned earlier for a lot of these things you rely on animal data and for mercury vapor there's not that much animal data. I mean, there's, I think -- I mean critically compared to methylmercury and some of the other developmental neurotoxins. So I think, you know, you're going to be at a loss for finding of these things that we're asking you to do.

I think the data would have to actually be, you know, built. You would have to actually, you know, provide some way of --

DR. JEFFCOAT: Well, that's why I --

DR. BURBACHER: -- getting the data, you know, generated.

DR. JEFFCOAT: We need to hear from Dr. Griffin and she's probably going to say what --

DR. GRIFFIN: I don't want to speak for my FDA colleagues, so please jump in, but I think perhaps we're reading more into the question than they are asking.

DR. JEFFCOAT: Yes.

DR. GRIFFIN: And I believe that the modeling here is going to be very simple. It's simply going to be exposure modeling.

DR. JEFFCOAT: Yes.

DR. GRIFFIN: It's not going to be able to take --

DR. JEFFCOAT: That's what's I was trying to say.

DR. GRIFFIN: It's not a pharmacokinetic model. So I think, again, I think they're basically looking for input on simple exposure assumptions, inhalation rates, body weights perhaps.

DR. JEFFCOAT: Age.

DR. GRIFFIN: Release of mercury from amalgam surfaces, number of amalgam surfaces, that kind of information. AHS.

DR. JEFFCOAT: Whether or not there is a pulmonary disease, for example?

Do we have consensus that that simple kind of model could be used with the caveat that all science changes over time and these numbers may change over time? Yes.

DR. JANOSKY: Yes, I have a comment and a suggestion for FDA and it actually taps directly into what we're talking about regarding how to do the modeling or how to think this through.

The question implies independence and I caution FDA and sort of the understanding of are these truly independent parameters or are they concomitant parameters, so that the number of surfaces, does it -- is the impact significantly different given the decade of life, as an example. So the concomitant understanding and the concomitant view should be, I would suggest, should be considered. As well as the independence in which this is to imply. So looking at these in concert, as well as looking at them independently.

DR. JEFFCOAT: Okay, we're about out of time for this question. I'm trying to get a sense of do we have consensus that we could do the simple model?

DR. BURBACHER: Not for maternal fetal. I just don't think we would be able to do it.

DR. JEFFCOAT: Oh, not for maternal fetal?

DR. BURBACHER: No.

DR. JEFFCOAT: Okay. Yeah. And Norm was -- Dr. Tinanoff, excuse me, was your statement, did that go with the question that's going to be asked later, which is the outcome or being able to -- you know, in children assessing the amount of mercury vapor actually --

DR. TINANOFF: Yeah, I don't think it can be done for maternal

fetal and also for young children.

DR. JEFFCOAT: No.

DR. TINANOFF: Maybe for older children maybe over age 3 or you can just do --

DR. JEFFCOAT: Okay.

DR. TINANOFF: -- simple arithmetic.

DR. JEFFCOAT: Yeah. Do we have consensus on this or are -- I'm seeing a lot of -- maybe you want to move on or? Okay, Mr. Watson.

MR. WATSON: That's great, thank you.

DR. JEFFCOAT: Okay.

DR. ZELIKOFF: Excuse me, Madam Chairman?

DR. JEFFCOAT: Yes, ma'am.

DR. ZELIKOFF: I'm here.

DR. JEFFCOAT: Ah, you're there. Okay.

DR. ZELIKOFF: I'm just not sure whether we adequately addressed with a yes or no for (c) and (d) and that had to do with the number of amalgam surfaces and filling size.

DR. JEFFCOAT: I think we put them in the model.

DR. ZELIKOFF: Okay. because my opinion would be yes.

DR. JEFFCOAT: Yeah.

DR. ZELIKOFF: It absolutely needs to be in.

DR. JEFFCOAT: Yeah, I think everybody when they said it --

DR. ZELIKOFF: Okay.

DR. JEFFCOAT: -- said it as almost a --

DR. ZELIKOFF: Okay. I just needed a yes or no. So I understand now.

So and the (d) in terms of are there other age related physiologic, genetic or pharmacokinetics, then I guess we all agree or some of us agree that genetic polymorphisms have to be included in the model? Some things like tissue deposition and excretion, male versus female, that maybe a sex parameter needs to be included in the model?

DR. JEFFCOAT: As we know what they are. That's why I said that it's going to be a moving target.

DR. ZELIKOFF: As -- okay.

DR. JEFFCOAT: Because obviously polymorphisms that are going to be associated with this are going to be --

DR. ZELIKOFF: Are an emerging --

DR. ZELIKOFF: -- are emergent field.

DR. ZELIKOFF: Okay. I just wanted to make sure that all four parts were addressed to --

DR. JEFFCOAT: Yeah. Thank you. No, you've done --

And I wan to assure everybody my notes are not the only notes; Clark is taking notes and the FDA is taking notes, but we want to make sure that we've captured -- tried to capture what everybody said and not just our own

opinions because, you know --

Okay, ready to move on. Reading the question.

MR. ADJODHA: Okay, this is Michael Adjodha again. I just wanted to clarify. So we've heard a lot of different parameters with regards to inhalation. And another method FDA used for assessing risk in a final rule is using urinary mercury concentrations. So this is a different method of -- different biomarkers. So this question concerns that.

In the final rule FDA considered urinary mercury levels as a biological indicator of mercury exposure. FDA compared urinary mercury levels in amalgam bearers to urinary mercury levels associated with preclinical nervous and renal system affects from occupational studies. FDA concluded that urinary mercury concentrations generally observed in adults and children ages 6 and older with dental amalgam restorations are approximately one order of magnitude less than the threshold levels associated with preclinical neurological and renal health effects in persons occupationally exposed to mercury vapor. The petitioners state that urinary levels are not accurate biomarkers of exposure and effects for mercury vapor.

Discuss whether urinary levels are an appropriate biomarker for assessing risk of exposure to mercury from dental amalgam. And part (b), how would the Panel recommend that FDA incorporate issues of bioaccumulation and clearances in assessing risk of exposure to mercury from dental amalgam?

DR. JEFFCOAT: Okay. Yes, Dr. Aschner.

DR. ASCHNER: I'll be brief again. I don't know if we have anything that's really better than urinary mercury so it's definitely probably the best bio medium that we have to measure mercury.

But what troubles me about framing this question, again, is that we're coming back to a very sensitive population where we have no information. It's stated here that urinary levels of mercury for children over the age of 6, and older populations are similar but I don't see anything about anybody that's younger than six.

MS. RUE: I have a comment.

DR. JEFFCOAT: Yes.

MS. RUE: Yes. I think we need to consider also that the varial population with decreased renal clearance and issues with creatinine that maybe need to be addressed and discussed and how that -- and is involved.

DR. JEFFCOAT: You said creatinine levels, did you?

MS. RUE: Well, with rising creatinine levels because --

DR. JEFFCOAT: Yeah, okay.

MS. RUE: -- they have decreased kidney function.

DR. JEFFCOAT: Yes, sir, Dr. Bates.

DR. BATES: Thank you. I agree. I think urine -- very often urinary mercury levels are some of the best things we have. But they're not always present in every study and I think we should not exclude other biomarkers. And they could be simple biomarkers like counts of amalgam fillings. I think we

shouldn't exclude that just because mercury was not measured. Another measure might be, sort of, amalgam surface years, you know, to -- as a measure of cumulative exposure.

Some studies, I think the Mimm study measured blood mercury levels. So I think we should be open to various biomarkers and try and make the connections between them because there's -- certainly there's data out there you can relate numbers of amalgam surfaces to urinary levels and blood mercury levels and so forth.

And I think Dr. Richardson's report is a table, I think it's Table 2 on page 26, which is -- he's gone through various studies and he's identified the relationship between urinary mercury levels and amalgam fillings and -- because they're a remarkable consistency, I think.

DR. JEFFCOAT: Yes, Dr. Griffin.

DR. GRIFFIN: I'll start by saying I think that's the best that we have right now. And I'm just going to throw out an observation and a wild speculation, in that when one looks at the Skaring (ph.) data, for example, that compares urinary concentration to number of dental amalgam fillings, and also the Sushi data, when you look at air concentrations versus urine concentrations, you see a very strong relationship above a certain level. But when you get down to the very low ends of the curve, that relationship seems to fall off. It's almost super linear.

So like I say, I'm just going to throw a speculation out there that

maybe there's a suggestion here of a threshold or you have some kind of binding going on internally, I don't know. But just an observation.

DR. JEFFCOAT: Yes, Dr. Kotagal.

DR. KOTAGAL: So as was mentioned yesterday, quantitative EEG, MR spectroscopy, and functional MRI maybe state of the art biomarker of toxicity. In addition to urinary mercury.

DR. JEFFCOAT: May I just ask you a follow-up question, just for the -- would you expect those to be in done in large populations that you would need to --

DR. KOTAGAL: No.

DR. JEFFCOAT: I'm just asking.

DR. KOTAGAL: No. No. But I --

DR. JEFFCOAT: You're the expert --

DR. KOTAGAL: Sure.

DR. JEFFCOAT: -- on that field.

DR. KOTAGAL: I don't think so. But I think there is so much debate and uncertainty about at what level of mercury is there harm in children that well-designed studies should be able to answer those questions. So I think that, you know, all these uncertainties would be removed if we are using studies which are well-designed because I think these tools will pick up synaptic dysfunction, brain dysfunction, well before there is a change in the psychological profile or development of clinical tremors. So I think by that point the harm may

have already been, so the point is --

DR. JEFFCOAT: That's true.

DR. KOTAGAL: -- we need to get to the -- to determining whether there is any dysfunction prior to clinical manifestations appearing. So for that reason I would submit these tools be considered.

DR. JEFFCOAT: Okay. And would you state again, would you want all the tools in the studies or --

DR. KOTAGAL: No, I --

DR. JEFFCOAT: -- say what --

DR. KOTAGAL: I think that EEG is a test of brain function.

DR. JEFFCOAT: Yeah. Um-hum.

DR. KOTAGAL: And MR spectroscopy is also actually -- it is a -- it will be able to measure, for example, levels of glutathione in the brain with the MR spectroscopy. So those -- I think that MR would give you a little bit about the brain anatomy also. So I think combining tests of brain functions or test the brain anatomy even would be reasonable to consider.

DR. JEFFCOAT: Okay. Yes, sir. And then I'm coming over --

DR. BURBACHER: I hate to stay on one note but I --

DR. JEFFCOAT: We need to hear from some other people because I don't want to --

DR. BURBACHER: Sure. I hate to stay on one note but if you're looking at in utero exposure, you know, these are not good biomarkers for

any -- I mean, if you think of how the first exposure from dental amalgams is going to be in the fetus, so you're going to start accumulating mercury in the brain, you know, before birth. So by the time you're 6 or whatever, you know, you've accumulated so much, you've cleared so much, none of these urinary levels are going to pick up any of that and of the effects that may occur, you know, prior to even your starting your post-natal studies.

So again, I think, you know, this is a good biomarker for what's going on with dental amalgams at the time but they -- I might be going down to (b) here. You're talking about figuring out what bioaccumulation, what kinds of long-term exposure may, you know, may have effects. You wouldn't expect to get a, you know, real clear correlation from a current urinary level.

DR. JEFFCOAT: Okay. Dr. Zelikoff?

DR. ZELIKOFF: I want to agree with Dr. Bates in that multiple biomarkers are the best way to go.

I also heard some description of effects and I think that looking at a biomarker of effect, rather than a biomarker of exposure, i.e. is mercury in the urine, I think that -- which is a biomarker, in my opinion, of a biomarker of exposure, but what I would really like to see which would make a better transition to an actual outcome, which we'll discuss later, is a biomarker of effect which might include porphyrin levels if you're going to look urinary.

I also agree with Dr. Burbacher and I think that there's been some evidence that cord blood might be a useful biomarker if you're looking prenatally

or fetally. Also since the urine of the fetus is in the amnionic fluid, although that has -- you have to be real careful because it changes over time, I think that could be considered. So I guess it depends on the age and it depends on whether -- I'm strong proponent of the biomarker of effect. It doesn't have to be EEG or something, you know, extremely dramatic; it could be something that again looks at a change that may cause an effect in an overall outcome. A very early change.

DR. JEFFCOAT: Yes.

DR. FLEMING: Yeah, Michael Fleming. I wanted to ask Dr. Griffin or Dr. Dourson, is there a relationship between urine mercury and symptomatology, or what we would call observable effects?

My understanding is that we have great variability in that. High urine mercury levels, the patient may not have any symptoms, very low excretion levels. They may have a lot of symptomatology. Is there any data to support the relationship between the observable effects and urine mercury levels?

DR. GRIFFIN: Yeah, I'm not quite sure how to answer that because the human studies that we have are not multiple dose studies; they're basically studies that looked at time-weighted exposures and different occupational settings, be it dentistry, fluorescent lamp factories, whatever. So they were able to equate effects to mercury in hair, mercury in blood, and mercury in urine.

No, there - as I mentioned earlier, you've got the Skaring data that shows you know, strong linear association between urine and mercury and dental amalgams. You have data that shows a strong relationship between urinary mercury and mercury in air. But that's as far as I can go based on the data.

DR. DOURSON: So just let me add a wee bit to that. The preferred way to go is biomarker data if you've got it.

DR. JEFFCOAT: Yeah.

DR. DOURSON: So you see the lead biokinetic model. Methylmercury, it's levels of methylmercury in blood. Cadmium, it's the amount of cadmium accumulated in the kidney. All biomarkers of exposure are tied to specific effects or lack of effects. And on the basis of, you know, the assessment is done.

In this particular case I haven't seen data that would allow FDA to do that. But if you would cobble those data together that sounds almost not the way to go but if you could put those data together in a way that would be helpful, that would be a preferred way to go. And so I would maybe defer to our FDA colleagues.

I know you've thought about this and maybe you've even attempted it.

DR. JEFFCOAT: Okay, what I'm hearing with respect to 3(a), okay, we haven't gotten to 3(b), is that the urinary mercury levels are not -- are the

best we have but we don't really consider them a gold standard -- my words, not words anybody's used around the table -- at this point. We would like to be able to get to the point where we can design -- have well-designed studies with the more high tech outcomes such as MR spectroscopy; is that --

DR. ASCHNER: I disagree with that.

DR. JEFFCOAT: You disagree with that?

DR. ASCHNER: Yeah, I do.

DR. JEFFCOAT: Okay. Who's talking? Okay, Dr. Aschner talking. Okay.

DR. ASCHNER: Yeah, these are very expensive studies and you might be able to do it in a very small population. I don't know --

DR. JEFFCOAT: That's what I was asking.

DR. ASCHNER: -- how you would do these studies with, you know, neonates. Well, you could do it with neonates; you couldn't do it probably or much more difficult to do -- measure glutathione levels in the fetus. I just don't know what road we're going down.

DR. JEFFCOAT: Okay.

DR. ISMAIL: Also, the same things is -- Amid Ismail -- we're not doing studies here because there's a policy decision that needs to be made and needs to be made within a short period of time.

DR. JEFFCOAT: Right.

DR. ISMAIL: And not to wait for 3 or 4 years to come up with a

solution. So what do we have today? What's the best marker? I think that it's integrated blood from both erythrocyte and plasma that's being measured and that could be used in some of the new studies being reported as another marker for effect.

DR. JEFFCOAT: Okay. Dr. Bates.

DR. BATES: I just want to say I'm not convinced that urinary mercury levels are better for example than a dental treatment history. So if you had a history of all amalgams that have been placed and how long they've been there, then that would give you maybe a better measure.

DR. JEFFCOAT: Oh, Doctor, what world do you live in? I'm sorry.

DR. BATES: I'm saying that --

DR. JEFFCOAT: I can't even tell you when all my fillings were placed.

DR. BATES: No, but there are dental records. There are dental records. And I've carried out a study which we used dental records and we had longitudinal record of placement.

DR. JEFFCOAT: I didn't mean to be --

DR. BATES: Yeah.

DR. JEFFCOAT: -- I meant to be --

DR. BATES: So -- and how many in which teeth and so forth. So these things do exist and just suggesting we don't overlook that possibility because there's not always mercury measurements available.

DR. JEFFCOAT: Yes.

DR. KOTAGAL: No, just in response to Dr. Aschner. No, I am living in an ivory tower. When I talk about MR spectroscopy it is done every day. It takes an extra 10 minutes to an MRI scan and we do it all the way down to newborns and it's a clinical tool. It's used every day almost by every neurologist in the country. So it's not something experimental. It is there. It's being used.

And you can measure glutathione. Why are we not measuring glutathione if we can? There are plenty of papers out there which talk about measuring MRS. I'm not talking about something that's ideal; I'm talking about something that's practical because the biomarkers for children, what are we using? Clinical exam? Neuropsychological assessment? Which are really not accurate measures of brain function in children. So children are not like adults. They're difficult to really determine effects, toxic effects, which is why one needs to resort to a --

DR. JEFFCOAT: Okay, again we're looking at measures of mercury exposure, not whether or not -- on this question, okay, not whether or not the mercury exposure caused damaged. We'll get there. They put them at the end. All right.

DR. KOTAGAL: Well, okay.

DR. JEFFCOAT: So you see what I'm saying? Because for exposure if someone --

DR. KOTAGAL: But exposure can be separate from effect in

children, so it's --

DR. JEFFCOAT: It can?

DR. KOTAGAL: I think the effect may vary so I think just simply looking at exposure without looking at effect -- we're assuming that children are the same as adults and --

DR. JEFFCOAT: Well, no, we said we weren't going --

DR. KOTAGAL: Okay. All right.

DR. JEFFCOAT: I think we said we -- I think we advised we weren't. I mean, it will be up to FDA as to what they finally decide but -- but we will get to your -- the question that everybody's dying to weigh in on. Yes.

DR. ISMAIL: I think when -- one thing we can comment on and this is similar to my comment from the last question, in that we can look back on the last Panel and what they recommended and our recommendations could be similar because I think what I'm hearing is are similar comments from the last Panel, review Panel and that there should be much more discussion of the limitations of these things than there has been in the past and not relying on them as proven markers of exposure.

DR. JEFFCOAT: Okay.

DR. ISMAIL: So I think that's, you know, that's one part of what -- of message that we can get to them. And you mentioned we need to do something quickly, so I -- you know, and it's consistent again with what has been said in the past.

DR. JEFFCOAT: So are -- we're discussing when urinary mercury levels, I know it's your reading of it, are an appropriate biomarker for assessing the risk of exposure of mercury from dental amalgam, what do we feel -- do we feel that is appropriate? I mean, that if we feel it's an appropriate measure, the answer's yes, okay. If we feel that we have caveats we should advise the FDA what the caveats are. I really haven't heard caveats except that we'll want to get to other things which are --

DR. ISMAIL: I think --

DR. JEFFCOAT: -- because it's the best we have.

DR. ISMAIL: Sorry. Amid Ismail. You've mentioned that this is not the gold standard, it's the best we have; it has limitations. But depends on the -- again, you can't look at a process without looking at the outcomes. When you look at the effects, what type of measures we use, urinary mercury levels are useful for certain effects for certain type of mercury, but for others you need to look beyond the urine and look at other markers.

So the question -- the answer is, yes, it is useful by not by itself.

DR. JEFFCOAT: Yes, Dr. Aschner.

DR. ASCHNER: When I answered my question I said my caveat was that I didn't see any data correlate urinary mercury levels in the age 6 and younger. And I think Dr. Burbacher, and I don't want to speak with him -- for him, but I'm not sure how urinary levels in the mother can be extrapolated to exposure in the fetus.

DR. JEFFCOAT: Yeah, and that -- that's a caveat we will -- yeah, that's why I'm trying to get consensus of the group on.

So let's see if we have consensus on this one. Okay. It's the best we have, so in adults and in older children we would probably use it. But it -- we don't have data and frankly it's nonsensical to use it in mothers for exposure for fetuses for pregnant women and not for children under 6, right? Do we have --

DR. BURBACHER: One suggestion would be get rid of the word "risk of" in the question because I think the risk is what's getting people to the effects. So assessing exposure to -- maybe we should say "Assessing current exposure to mercury from dental fillings"?

DR. JEFFCOAT: Yeah, that's all it can tell you. Is that --

DR. BURBACHER: I mean, I don't know if that -- I'm not sure if that's changing --

DR. JEFFCOAT: Is that acceptable --

DR. BURBACHER: -- the whole question.

DR. JEFFCOAT: -- to FDA if we take --

MR. WATSON: Yes. Actually, we were just talking about that. That's fine.

DR. JEFFCOAT: I think that --

MR. WATSON: If it helps get us moving forward --

DR. JEFFCOAT: Yeah.

MR. WATSON: -- please do so.

DR. JEFFCOAT: Okay, so we're going to remove the word "risk" from the question.

DR. BURBACHER: And put in "current exposure."

DR. JEFFCOAT: Okay. Do we have consensus on (a)? Yes, sir.

DR. KOTAGAL: One point. Do you -- I know the cutoff is 6 and below. Actually in children we go by puberty and pre-pubertal is a better marker for metabolism and metabolism changes shortly around there, so I mean, I don't see a whole lot of difference between the metabolism of a 5-year old versus an 8-year old and it's -- you know, unless the data's really compelling, that all pre-adolescents or pre-pubescent children be combined so that rather than using 6 and below I would say pre-pubertal and below.

DR. JEFFCOAT: I have to ask -- bring this to the experts in the area. Dr. Aschner.

DR. ASCHNER: So again, I would submit that I would disagree that a 3-months old baby is different from a -- is similar to a 5-year old.

DR. KOTAGAL: Well, that's true. That's true, too.

DR. ASCHNER: Because many of the systems for mercury excretion might not be 100% functionally. The blood/brain barrier is not mature. So maybe a 5 and 6-year old might be the same but a 2-months old and 6-months old are going to be different.

DR. DOURSON: A question?

DR. JEFFCOAT: Yes.

DR. DOURSON: Michael Dourson here. Just a question for Dr. Burbacher. When we do risk assessment and we're looking at fetal exposures we often look at the exposure to the mother, which in effect is the exposure to the fetus. If we're not using maternal urinary levels as a measure of fetal exposure, what are you suggesting that we do? Is there another thing that we can look at assessment folks?

DR. JEFFCOAT: Well, he's just saying you can't do it with this.

DR. BURBACHER: Yeah, I -- you know, again, I think a lot of times you rely on animal data and you could build maternal fetal kinetic models. They've done it with methylmercury using animal data. So -- and again that's where we have a dearth in this for mercury vapor. We really don't have -- usually have a lot of weight of evidence in animal -- with animal data to support the RfC or the RfD; here we really don't have that. So that would be one way.

I think just in studies that are going to start from now on, I mean, I think it's just very important that they find out, you know, at least the maternal numbers of amalgams or something like that would be worthwhile knowing. You know, you could do urine but I don't know how good of a marker that would be.

DR. DOURSON: Thank you.

DR. JEFFCOAT: Okay. I'm not quite sure whether we have consensus at leaving it at under 6 years or under puberty because there's a big difference in the teeth that Norm could -- Dr. Tinanoff could discuss for us for how it might wear on the amalgam.

DR. TINANOFF: I'm going to --

DR. JEFFCOAT: Maybe.

DR. TINANOFF: -- defer to others on whether we're going to use a cutoff at 6 or pre-pubertal. Actually to me it seems like they're two -- there are several levels for children, maybe from 0 to 3 -- maybe in utero; 0 to 3; 3 to 6; and 6 to puberty?

DR. BURBACHER: How early do they put in --

DR. ISMAIL: Madam Chairman?

DR. BURBACHER: I mean, do they put amalgams in --

DR. JEFFCOAT: Wait a minute, I'm just writing this down. Okay, who --

DR. BURBACHER: Do they put amalgams in 2-year-olds?

DR. DOURSON: Oh, yeah.

DR. JEFFCOAT: -- called me?

DR. BURBACHER: Really?

DR. ISMAIL: I called.

DR. JEFFCOAT: You did. Thank you, Dr. Ismail.

DR. ISMAIL: I do agree 100% with Norm.

DR. JEFFCOAT: Yeah.

DR. ISMAIL: 0 to 3 is a unique age and where usually are treated in the OR under anesthesia and receive a lot of restorations. So 0 to 3 is a unique age; and then 3 to 6; and above 6.

DR. JEFFCOAT: But we're probably not looking at in utero in this? In the exposure?

DR. TINANOFF: That would be a separate group. Separate group.

DR. JEFFCOAT: Well, you would have to build a separate model and we're not even sure that would work, right? Okay. All right, that's all right.

Okay, yes, and then we're going to go on to (b) because you're not going to eat till we finish (b).

Dr. Griffin. Oh, you had a question, didn't you? I thought. Oh, no, I didn't cut you off, I just --

DR. GRIFFIN: Oh, I do not want to reopen (a) but I was just expressing a concern. We need to be careful how we word these because it's really a lack of knowledge regarding less than 6 years old, as opposed to knowing. So make sure that that's communicated, please.

DR. JEFFCOAT: Okay, remember we're not doing a written report to FDA. This is what we're presenting to Mr. Watson.

And may I do 3(a) and we'll do 3(b) separately for you to find out if this is acceptable to you?

MR. WATSON: I'm sorry, I did not catch what you just said.

DR. JEFFCOAT: Oh, I just want to ask you if our answer to the Question 3(a) is acceptable, which is we do have consensus that urinary mercury levels are the best we have for measuring exposure but we do need to subset out groups of children: fetuses in utero; children from 0 to 3; 3 to 6; and 6 to

puberty.

MR. WATSON: Yes, that would be fine.

I think one of the things that I wanted to point out was again going back to what I said earlier, the stratification and strategy will be based on what we have now and what we have to do later. So I'm hearing some information that this is what we would like to have and I'm just -- want to make sure that it has to do -- that there is some -- when we go back we're going to have to see what we actually do have and base it on that type of thing.

DR. JEFFCOAT: Of course.

MR. WATSON: So the timing is always going to be important for us. So yes, the answer is fine for right now, thank you.

DR. JEFFCOAT: Okay. It has been suggested by -- oh, and I'm going to -- suggested by Olga that we take lunch now if you'll all promise to stay on the question when we get back, okay, whichever question it is. And we're going to take your comment before, because I assume that you had something.

DR. BURBACHER: So I mean, I had, I guess two things. One is we -- I had suggested that they -- that we put in current exposure to mercury to distinguish it from any kind of a marker for bioaccumulation because, I mean, what we have is --

DR. JEFFCOAT: Yeah, that has --

DR. BURBACHER: -- what we have are data from, you know, from urines that indicate that it corresponds to current air levels or something; it

doesn't correspond to how many years.

DR. JEFFCOAT: Yeah, they're editing that question --

DR. BURBACHER: So -- okay.

DR. JEFFCOAT: -- anyway, so I'll give that to them.

DR. BURBACHER: Okay. And then the second part was just, I guess, reiterating is that I think the comments should indicate that we think it's the best, but make sure that the limitations, you know, are really described because that's where I think things fall off. I think that's where things can fall off in terms of what the limitations are.

DR. JEFFCOAT: Okay.

DR. ZELIKOFF: Can I just add --

DR. JEFFCOAT: Folks --

DR. ZELIKOFF: It's just one small comment.

DR. JEFFCOAT: I know, except that we --

DR. ZELIKOFF: Just for the -- I'm sorry, for the in utero I'd like just to consider that cord blood might be a viable biomarker for maternal exposure, fetal exposure and that wasn't included in the summary.

DR. JEFFCOAT: But there is no data, right?

DR. ZELIKOFF: There is very little data. The only data that does exist in that is with methylmercury.

DR. JEFFCOAT: Right. That's what I thought. Okay.

Okay, we need to go to lunch, folks.

UNIDENTIFIED SPEAKER: Madam Chair, when are we returning?

DR. JEFFCOAT: We will be back --- we need to come back in 1 hour, which is -- yeah, we will now break for lunch. Panel members? Folks? Listen. Panel members, do not discuss the meeting -- I know you could repeat this with me now -- topic during lunch, amongst yourself, with any member of -- or with any member of the audience. We will reconvene in this room in 1 hour. Actually, we'll reconvene at --

(Whereupon, at 12:27 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:20 p.m.)

DR. JEFFCOAT: I want to remind people that I'm taking notes of all of your comments, Clark is doing backup notes, and the FDA is doing a third set. So the comments you've made have been captured on paper that are not part of that, sort of, two sentences that we got Mr. Watson's okay on, okay?

Excuse me?

(Inaudible.)

DR. JEFFCOAT: Oh, Joel White. Oh, okay. Clark is doing it, that's right.

UNIDENTIFIED SPEAKER: But I got it. We're capturing it all.

DR. JEFFCOAT: Okay. In other words, we have more than one person capturing it. And the goal is not just to have a single -- but remember, we're not here to design long-term trials.

Okay, (b): How would the Panel recommend the FDA incorporate the issues of bioaccumulation, which is where some people went in the last question, and clearance in assessing mercury exposure from dental amalgams? And I took "risk" out again because we took it out of the previous one. Bioaccumulation and clearance, how would that be assessed? Ah, yes, Judith.

DR. ZELIKOFF: Just a short comment on that. I think given the differences between the sexes, I think sex is an important variable since females don't have as much accumulating in the kidney as the male. I think there's a

sexual dimorphic aspect that has to be included.

DR. JEFFCOAT: Yeah. Well, I think, unless people disagree, the model we talked about before, you could use the results of that in this but what are the variables that might be existent in databases, okay, or relatively straight forward to get, would we want to recommend to the FDA that they use to look at bioaccumulation and clearance? Anybody? We don't have any?

DR. BURBACHER: You don't have the data, I would think. I mean, unless you've done studies where you've taken out all the amalgams and followed people for months as their urinary levels go down. I've not seen any of that. I mean, this is another, I think, limitation from not having any animals. This is where animal data could actually inform a lot of these parameters. And again, I don't know of any for mercury vapor. There's a lot for methylmercury. Some for thimerosal, too.

DR. JEFFCOAT: Yeah, but we're talking about --

DR. BURBACHER: Not for vapor.

DR. JEFFCOAT: Let's stay on the topic. I'm -- just because, folks, you don't get to go home till we finish. Yes?

MS. DE LUCA: Would there be any data by organ site? If we're looking at certain organs, we're looking at where it's going, so does anybody own current data on organ site?

DR. JEFFCOAT: Well, what would we have that would look at kidney, for example?

MS. DE LUCA: Kidney's the one, main one I was thinking of.

DR. JEFFCOAT: Okay.

MS. DE LUCA: I don't know.

DR. JEFFCOAT: Creatinine levels? Mercury in the urine?

MS. DE LUCA: Um-hum.

DR. JEFFCOAT: I'm just throwing out stuff that I know is there.

MS. DE LUCA: Exactly.

DR. JEFFCOAT: I mean --

MS. DE LUCA: I just don't know who would house it.

DR. JEFFCOAT: I'm not the expert in this field, at all; you guys are. Dr. Aschner?

DR. ASCHNER: Yeah, I'm not sure, what do you mean exactly by clearance because there is no cessation of exposure so clearance and a biomarker of exposure in this case would seem to be the same thing. FDA?

DR. JEFFCOAT: It was as we defined it.

DR. GOERING: I think our main concern with this question, and you have a good point, Dr. Aschner, I think the main goal of this question was to address issues of bioaccumulation of mercury. It's known that mercury will slowly accumulate in several tissues, at least over time, and how do we factor that in when urinary mercury, some people believe, may not reflect that continuing increasing concentration in tissues? Might go back to urinary mercury as an appropriate biomarker, not does it actually reflect --

DR. ISMAIL: I mean, there might be some issues with susceptible populations where the clearance of mercury might be slower compared to the general population but I think even for that type of subpopulation we don't have the data, you know. So I'm not sure how you could look at bioaccumulation short of look at specific organs, which is obviously is not amenable.

DR. JEFFCOAT: So you would be talking about biopsies, for example?

DR. ISMAIL: Yeah, I mean --

DR. JEFFCOAT: I'm trying to --

DR. ISMAIL: Yeah.

DR. JEFFCOAT: -- capture your thought. Okay.

DR. FLEMING: Yes, Michael Fleming. I wanted to address this to the FDA. This part (b) was asked in the context of risk and not exposure, necessarily; is that correct?

DR. JEFFCOAT: Well, we took the "risk" out.

DR. FLEMING: You took the word "risk" out.

DR. JEFFCOAT: Because we took it out of (a) and they were the same -- part of the same thinking.

DR. FLEMING: I'm just wondering, the patina on the question really has more to do with the issues of bioaccumulation and clearance in assessing risk, even though we took it out, which is why I think you asked it.

MR. ADJODHA: Yes.

DR. FLEMING: So by taking it out --

DR. JEFFCOAT: Do you want it in?

DR. FLEMING: -- what are we offering you here?

DR. JEFFCOAT: I don't think we can answer it.

MR. ADJODHA: Yes, I think that's correct.

DR. BURBACHER: I think "risk" belongs in this.

DR. JEFFCOAT: "Risk" belongs in this one?

MR. ADJODHA: Yeah. Yes.

DR. FLEMING: I think it belongs in this question. Not necessarily (a), but I think it belongs -- because the entire context changes.

DR. JEFFCOAT: Yeah. They're different questions.

DR. FLEMING: Does that make -- does that sound good?

MR. ADJODHA: Yes, that's correct.

DR. JEFFCOAT: Okay.

DR. BURBACHER: So there are, if you just think about where the mercury ends up and what form it is, I think everybody agrees that once it gets to the brain it's inorganic. And that doesn't matter whether it's methyl or thimerosal or mercury vapor, it seems. And we do have a little bit of data on inorganic mercury half-life and it's like a year or two. So, but that data's fairly limited and it's from monkeys. There are some data, I think, from rodents, as well. But it is a lot longer than the organic form. So it would be, you know, the best estimates, which aren't based on that great of data, would be a year or two.

DR. JEFFCOAT: Okay.

DR. DOURSON: I have a question.

DR. JEFFCOAT: Yes.

DR. DOURSON: Michael Dourson here. So just a question to my FDA or Panel colleagues. Yesterday I seem to remember someone saying that there is a great excretion of mercury in the feces.

DR. JEFFCOAT: That's what they said.

DR. JEFFCOAT: And I got the impression that it might even be more than in urine. Are there studies in humans on this? How did we come to that statement yesterday? I'm missing the recollection of that.

DR. JEFFCOAT: That was a study in four monkeys, according to my recollection.

DR. DOURSON: Okay.

MR. ADJODHA: Yes, that wasn't our statement, I believe that was a presentation by Dr. Anne Summers.

DR. DOURSON: So then the question is do we have those comparable data in humans? Is that where most of the excretion is?

MR. ADJODHA: Step up to the mic, please.

DR. JEFFCOAT: Are you asking her?

DR. DOURSON: Oh, I would love to -- for her to answer.

DR. JEFFCOAT: Okay, that's fine. We just have to follow protocol.

DR. SUMMERS: I understand. I understand.

DR. JEFFCOAT: And state your name, please.

DR. SUMMERS: Yes, right. Anne Summers, the University of Georgia.

DR. JEFFCOAT: Right. We actually worked with eight monkeys and we did this in collaboration with Fritz Lorscheider and Murray Vimy in Canada, and all of those studies are published extensively and I can provide you with references. And the fillings were placed and then removed in all but two of the monkeys, and the latter two monkeys, one of which I showed the other day, the fillings stayed in. So there is -- not huge population studies, but they were very thorough studies.

And then with respect to people, there are Swedish studies and I think Finnish studies that actually followed on those studies for the purpose of evaluating that question explicitly in humans. And what they followed, I believe, was urine and possibly blood mercury in more than 10 and less than 100, and I don't remember the exact number, of humans who were coming in to have their fillings removed. And so they had -- they have good DMF data on them and they have -- they have at least urine measure and blood measure on -- but those are the only data that I know of on removal in humans. There may be other ones.

But those are for a long time the, sort of, standing ones from our animal studies.

DR. DOURSON: Thank you.

DR. JEFFCOAT: Okay. Let's try and get to the question. And I

think it's a hard question, frankly. What would we want to see the FDA look at --

Oh, you, Joel, I'm sorry.

DR. WHITE: Well, I'm a dentist. I'm not a urologist. But it would seem like some other measure of kidney function would be appropriate because people who have impaired kidney function are going to have difficulty cleaning and then the accumulation risks go up. So knowing some other marker or measure of kidney function.

DR. JEFFCOAT: Okay. What other markers? Yes.

DR. ASCHNER: I mean, the urinary excretion is usually collected for creatinine. I'm not a physician but that would seem to me the controls --

DR. JEFFCOAT: You've got to do creatinine.

DR. ASCHNER: -- for kidney function.

DR. JEFFCOAT: Okay. Yes.

DR. BURBACHER: I guess I'm a little confused in that, I mean, you would actually need to design studies, clearance studies. I mean, they have a specific design to them that most probably everybody knows, you know, to get clearance data. And, I mean, are there -- you probably looked; I mean, are there any out there?

DR. JEFFCOAT: No.

UNIDENTIFIED SPEAKER: We didn't review them if there are.

DR. BURBACHER: And it's the same way with bioaccumulation. I mean, the bioaccumulation issue can be -- the bioaccumulation can be very

different on the uptake, when you're first starting getting exposed; the rate of bioaccumulation can be much greater than if you get steady state or during the clearance. So that can change, as well. It's not as constant. So these studies, you know, are pretty, you know, specific to these kinds of questions and I think without those types of studies I'm not sure that doing creatinines or anything of that -- would give you much.

DR. JEFFCOAT: Um-hum.

DR. BURBACHER: I mean, you would need the clearance parameters somehow and you do that by doing clearance studies.

DR. DOURSON: I'd like to ask Dr. Summers again if your monkey studies gave that clearance kind of information? You have urine, you had feces, you have the extracted tooth.

DR. SUMMERS: Not yet. The data that I --

DR. JEFFCOAT: Yeah, I need to recognize you.

DR. SUMMERS: Anne Summers.

DR. JEFFCOAT: Wait a minute.

DR. SUMMERS: I'm sorry.

DR. JEFFCOAT: I'm sorry, it's just protocol. Okay.

DR. SUMMERS: No, no, I -- that's fine.

DR. JEFFCOAT: Dr. Summers, would you --

DR. SUMMERS: Thank you very much.

DR. JEFFCOAT: -- help us with that question?

DR. SUMMERS: Anne Summers, University of Georgia. Those data were taken by the Lorscheider Group, which are physiologists. I should mention that there's also one or more sheep that they did extensive studies on, and I gather that sheep have a digestive system that's -- or some systems that are -- that resemble those in humans.

So multiple organ -- many of those studies, or at least four of those studies, four of those animals were done with isotopic mercury and mercury was assed in many organs and fluids. And those were done in the early '90s. And then the work that we did with them on the various monkeys stretched through the '90s and there were physiological data that were published on about half of those monkeys, and they're in the literature. And that includes organ loading with isotopic mercury.

And the mercury data that I showed you were data that were fecal data that were collected because our interest was in the microbial community, which of course is capable of metabolizing mercury so that it's reabsorbed in the gut, either as mercury (0) or mercury -- methylmercury --

So yes, those data are there. They are in those papers. And I would very happily pull those and send them to the Chair or whoever's interested. I think I have to communicate through the Chair and I will happily do that.

DR. DOURSON: Thank you.

DR. JEFFCOAT: But to reiterate what I think heard here, though,

we don't have extensive data in humans?

DR. SUMMERS: Yeah. I don't know of any post-amalgam removal organ data in humans. At best it would be urine and blood. But I -- and I don't think there's any fecal data.

DR. JEFFCOAT: Thank you, Dr. Summers.

So I think our answer to that question is we don't know; is that -- do we have --

DR. BURBACHER: I think it's -- I think again it's a limitation that when they are talking about urinary levels and how they represent exposure and body burden, these are all limitations where they really will be limited in how they talk about that because they don't know about bioaccumulation; they don't know about clearance.

DR. JEFFCOAT: Thank you, Dr. Burbacher.

So do we have consensus that we really do not have the information to answer that question? Mr. Watson, is that an acceptable answer?

MR. WATSON: Yes, that's the answer.

DR. JEFFCOAT: Okay.

DR. FLEMING: May I add just one clarification?

DR. JEFFCOAT: Okay.

DR. FLEMING: If you don't mind?

DR. JEFFCOAT: Doctor, you really need to say your --

DR. FLEMING: I think we can acknowledge --

DR. JEFFCOAT: -- name, Dr. Fleming.

DR. FLEMING: Pardon me?

DR. JEFFCOAT: Please say your name.

DR. FLEMING: Mike Fleming, sorry.

DR. JEFFCOAT: I said it for you, but --

DR. FLEMING: I think we can acknowledge that there is bioaccumulation and clearance differences. I don't think there is debate about those two issues if I understand the Panel correctly. But what we lack are data to establish the nature of the bioaccumulation phenomenon and the clearance issues that vary between subgroups and all the rest.

DR. JEFFCOAT: Yeah. They want to know how they would incorporate that.

DR. FLEMING: That.

DR. JEFFCOAT: And so we need to know that.

DR. FLEMING: And since we don't have data --

DR. JEFFCOAT: Right.

DR. FLEMING: -- it would be hard for them to do that.

DR. JEFFCOAT: Okay, we're on to Question Number II, thank you. And if we can hear from the FDA what Question Number II is?

DR. GOERING: Peter Goering, FDA. In this next section of questions we're going to be asking about reference exposure levels. In the first

part we're going to be asking about the critical study used to set the LOAEL or NOAEL. In the second question we'll be talking about the uncertainty factors and which are most appropriate. And in the last one we're going to be asking for assessments about the various reference exposure levels.

In the final rule FDA relied upon the U.S. Environmental Protection Agency's reference concentration for chronic inhalation exposure to elemental mercury vapor for assessing the risk of mercury exposure from dental amalgam. And I refer you to a table at the end of your packet of questions for a comparison.

The petitioners state that the EPA reference concentration for elemental mercury is not sufficiently protective. The critical studies selected by EPA (Fawer et al. 1983), evaluated workers exposed to mercury vapor in three different industries: chloralkali, acetaldehyde and fluorescent tube manufacture. It has been suggested that concomitant exposure to chlorine gas in the chloralkali occupational setting can modify the response to mercury vapor resulting in a higher LOAEL. Rather, a dental professional occupation exposure study was selected by Richardson et al. as the critical study for deriving a reference exposure level for mercury vapor.

The first question then is: Discuss the selection of the critical study to determine a reference exposure level for mercury exposure from dental amalgam. Discuss the strengths and weaknesses of each key study and the appropriateness for selection as the critical study for determining the reference

exposure level for mercury exposure from dental amalgam.

And the first sub question is: What is the strength of evidence that the exposure-response relationship for mercury vapor is modified by concomitant exposure to both mercury vapor and chlorine gas?

DR. JEFFCOAT: Okay. So the first step, this question has a lot of sub-questions, so let's take them one at a time and if people want to modify what we can -- what they want to do that's fine.

Hold on a second, okay? Let me just state what we're talking about and then we'll -- then I'll be right with you, Dr. Griffin.

State the selection of the critical study to determine the relative exposure level for mercury from dental amalgam, Okay. And they said "the critical study," but then they say, and so I wanted to ask you, "discuss the strengths and weaknesses of each key study." Do you want a chart of the studies or do you want the key study?

(Inaudible.)

DR. JEFFCOAT: What? Yeah, the question is to the FDA.

DR. GOERING: The slide with the comparisons of the various reference exposure levels are on the slide. I did not include the Lettmeier et al. paper that was discussed yesterday.

DR. JEFFCOAT: That was just published. So we --

DR. GOERING: And the two studies that are related primarily to this question are the -- the two studies are the Fawer et al. studies, which you

see under the "EPA RfC" and "ATSDR" column, and the Canada REL that Dr. Richardson used, based on a critical study that he identified Nimm et al., 1992, which was primarily only dentists in the study.

DR. JEFFCOAT: Okay. Comments from the Panel? Yes, Dr. Griffin.

DR. GRIFFIN: I would like to -- I'd like to correct something here before we go on because it's going to have a big impact. The statement that the quantitative reference concentrations based on chloralkali workers is wrong. As mentioned earlier, there's a qualitative and a quantitative aspect to development of a toxicity value.

When we amassed the literature, the predominant occupational studies were chloralkali workers, and from those studies it was determined that neurological effects were the critical effects.

The next step was then to develop a critical effect level. Three studies were used to develop the critical quantitative effect level. Approximately 250 people total from the 3 studies, of which only 12 were chloralkali workers, the rest were dentists, fluorescent lamp workers. And so this issue about the interference of chlorine with the mercury, it's a red herring. It's really not worthy of this Panel to have to discuss. The issue of Nimm versus Fawer is really a silly issue because Nimm was one of the studies used to develop the EPA reference concentration.

So I just wanted to set the record straight before we proceed down this path. And this is not opinion; it's page 5 of the IRIS chemical file for

elemental mercury.

DR. JEFFCOAT: That's very helpful, thank you.

Do we have other comments? Yes.

DR. ASCHNER: My question is actually for Dr. Griffin. Did you say that this was based on neurological effects? Why would it based on neurological effects and not more sensitive organs like kidney?

DR. GRIFFIN: The bulk of the literature was evaluated. Again, if you go to the IRIS chemical file you will see that there are also studies that do at look at renal function. We looked for the effect which was occurring at the lowest doses consistently in the population and the central nervous system effects were occurring at much lower doses than the renal effects. And again, it's in the file.

DR. JEFFCOAT: Yes, Dr. Ismail.

DR. ISMAIL: To move the discussion forward, I think we --

DR. JEFFCOAT: Yeah, we need to --

DR. ISMAIL: -- we accept what Dr. Griffin has said; however, there is a need for update of -- update of the literature to do a review from 19- -- I think last study was in the '80s -- to update from 1992 until 2010 what was -- has been published that could contribute or add to the body of -- the weight of evidence that you have, the EPA have used. And that's --

DR. JEFFCOAT: Other comments?

DR. DOURSON: I have a comment.

DR. JEFFCOAT: Yes.

DR. DOURSON: Michael Dourson. I concur with Dr. Griffin. The IRIS file is clear in its interpretation; it is multiple studies.

DR. JEFFCOAT: Other comments? Oh, sorry.

DR. BATES: Michael Bates. I agree with Dr. Ismail that the studies that are being considered are pretty old and there are some newer studies. And one thing I would like the Panel to consider is the possibility of using a more continuous relationship than just simply compare -- studies which compare an exposed group with an unexposed group. And one the speaker's used today, Dr. -- I'm blanking -- Ginsberg, yes, mentioned that. And he also mentioned the study by Echevarria et al., and actually that gives a continuous relationship. This actually has more information than just comparing one group with another. So of course, this might not lead its -- lend itself to an RfC or an REL but nonetheless there is more information in it when you look at a continuous measure.

And I believe there are other studies probably out there that, you know, have these -- this continuous data. And particularly if the data could be combined across studies it could be very helpful.

DR. JEFFCOAT: Obviously, just to finish your sentence, which is a fault I sometimes have, you have to -- the data has to be in a format where you could do that because some older studies don't always have the data in a format where you can tell.

DR. BATES: Meaning? You mean the continuous data?

DR. JEFFCOAT: Yeah.

DR. BATES: Yeah. But we do now have the Echevarria study. Possibly some others. And we should consider whether we could use that. It might require a different approach in just calculating a REL.

DR. JEFFCOAT: Okay. May I ask FDA a question? REL, is it not by definition a cutoff? A number? Or is it a relationship? Just so that we know what we're answering, because they're right, that's a more powerful statistical analysis. But we need to answer your question.

DR. GOERING: Well, I could ask Dr. Bates to elaborate on his definition of continuous, but I'll go ahead and try to answer your question. Your question is, is an REL a specific cutoff?

DR. JEFFCOAT: Well, or a range? You know --

DR. GOERING: Okay, it's not a bright --

DR. JEFFCOAT: -- maybe .2 to --

DR. GOERING: As I understand it, it's not a bright-line threshold.

DR. JEFFCOAT: Um-hum.

DR. GOERING: There is, as we've heard, an order of magnitude difference. As far as I know it is the only tool that we have to do this kind of comparison. Dr. Dourson mentioned a benchmark dose study where we would have to have raw data and --

DR. JEFFCOAT: That's --

DR. GOERING: -- it's a better approach, and if that is what

Dr. Bates was referring to, that kind of data, if it exists it would be appropriate to do it. But without that kind of data we rely on the reference exposure level approach. Not "we" but other agencies, as well.

DR. JEFFCOAT: Yeah. And my concern was whether or not the raw data is -- but that one just has to look into it.

DR. BATES: Well, all I can go on really is the paper or the papers by Echevarria and it appears they have the data.

DR. JEFFCOAT: Um-hum.

DR. BATES: And presumably it could be accessed. I can't see why not. And if they were willing to assist, it seems to me it would be a better approach.

DR. JEFFCOAT: Yes, Ken. Dr. Anusavice.

DR. ANUSAVICE: I don't have the paper in front of me but there's a quote from the paper that, where they concluded that: We were unable to simultaneously control for all possible confounders, which would have made the results too unstable -- I'm not quite sure what that means -- small size of the exposed test group also allows a few individuals to have a considerable impact on some results.

So I'm not sure how we take into account any confounders that would go into this continuous analysis?

DR. BATES: I guess it depends on what data they do have. But you know, we -- as epidemiologists we're used to adjusting these sorts of data to

take that sort of thing into account. So without actually knowing exactly what they have, but they probably have as much as Nimm and Fawer have. I suspect.

DR. ANUSAVICE: Except their sample size was an n of 19; is that sufficient?

DR. BATES: Which are we talking about?

DR. ANUSAVICE: Oh, I'm sorry. Forget it.

DR. BATES: Echevarria has several hundred.

DR. ANUSAVICE: I'm going back to the other -- yeah.

DR. JEFFCOAT: Yeah.

DR. BATES: And a -- so it's a bigger study than both of those studies combined. So it would be a pity not to use the data. But, you know, we could not analyze it here in this meeting, we would have to seek the cooperation of Echevarria and maybe some other investigators.

DR. JEFFCOAT: Dr. Burbacher.

DR. BURBACHER: Well, the previous comment when this came up at the last meeting, because you can see it in the response to the last Panel, was that there's aren't any -- they actually correct the way they say it, there aren't any non-exposed occupational subjects in their study. So there aren't folks within the occupation that were doing something else that would not have exposed them to the mercury vapor, so everybody's exposed, and that was considered, I think, a critical flaw for using it for risk assessment.

DR. BATES: If I can comment? Michael Bates again. I didn't see it

necessarily as a critical flaw. I mean, they have a range of exposure, it's clear. And if we can look at that dose-response relationship. Some people have very little exposure, some people have a lot. And so I still think there's a lot of information in here that we could usefully use and it will be a great shame not to.

DR. JEFFCOAT: Okay. I'm trying to figure out what our consensus is here so help me, all right? We really would like to update the literature. And much of what has been asked for is in the IRIS file. But we're not -- we agree with the homework assignment that suggested that the analysis be linear, rather than looking for a specific cutoff, but obviously we can't tell FDA that's absolutely going to yield results because we don't even know if they'll give us the data. I have to put that into better words but --

DR. DOURSON: Pardon me. Just a brief comment. I was only referring to question 1(a).

DR. JEFFCOAT: 1, yeah, that's where -- right.

DR. DOURSON: Which was the Fawer.

DR. JEFFCOAT: Right.

DR. DOURSON: And I do have commentary by Dr. Aschner's and Bates, which is subsequent questions.

DR. JEFFCOAT: Right.

DR. DOURSON: So I -- I actually think the consensus on 1(a) is pretty clear unless someone -- because we're talking about that particular study

and mercury vapor and chlorine gas confusing it.

DR. JEFFCOAT: Right, that Dr. Griffin's correct in what she said?

DR. DOURSON: Right. So I --

DR. JEFFCOAT: You're agreeing with her?

DR. DOURSON: Oh, I'm agreeing.

DR. JEFFCOAT: Yeah. Yeah.

DR. DOURSON: And I don't hear any disagreement, so --

DR. JEFFCOAT: I don't think anybody's disagreeing.

DR. DOURSON: And all the other discussion points are really good. I would like to contribute at the appropriate time to them.

DR. BURBACHER: But I mean, we need to answer the question in a certain way because it's asking --

DR. JEFFCOAT: Right.

DR. BURBACHER: -- it's asking are there data that would indicate that the evidence for the change; its' not - and it's not asking whether that was the only study or not, so --

DR. DOURSON: Right, so that's a very limited question. 1(a) is a very limited questioning.

DR. BURBACHER: Right.

DR. DOURSON: And I think it's been asked and answered and no one's disagreeing with Dr. Griffin.

DR. BURBACHER: Right. But she's not indicating that mercury

vapor is not modified by concomitant exposure. Okay.

DR. DOURSON: Well, I think the --

DR. JEFFCOAT: Let's let Dr. Griffin restate what she said --

DR. DOURSON: Partly.

DR. JEFFCOAT: -- so everybody's not stating it for her since she's sitting here. If you don't mind, gentlemen?

UNIDENTIFIED SPEAKER: I have her summary from the lay -- for the lay person maybe?

DR. JEFFCOAT: Okay.

DR. STANFORD: That basically the chlorine gas is a distracter, the IRIS file is clear and multiple studies were used.

DR. JEFFCOAT: Right.

DR. BURBACHER: Right, but we're not saying anything about --

DR. JEFFCOAT: Is that --

DR. BURBACHER: -- it doesn't modify it.

DR. JEFFCOAT: Have we got it?

DR. GRIFFIN: That is correct. So the question is irrelevant.

DR. DOURSON: Okay.

DR. JEFFCOAT: Okay. So on to question 1(b): Discuss the strengths and weaknesses of the EPA reference concentration with respect to the general population and sensitive subpopulations.

DR. DOURSON: Okay, Michael Dourson here.

DR. JEFFCOAT: Yeah.

DR. DOURSON: Okay, this is a great question and really one of several nubs that we have to come to. The reference concentration is intended to address sensitive individuals and by definition everybody else. Sensitive individuals protected, so was everybody else that's not sensitive. So that's the intention.

But Drs. Farland and Ginsberg have pointed perhaps a weakness of the EPA RfC in that an uncertainty factor of 3 for within human variability was used only. And Dr. Griffin said in addition of the uncertainty factor of 3 for database uncertainty factor was used, which actually does account for testing in young people, children, and neonates. So there is that weakness.

If we are to relook at that particular uncertainty factor, there's two ways you could do it. You can say, well, we would really like to see a 10-fold as a default, actual data replacement would be best, for that within human variability uncertainty factor of EPA. That is consistent with both ATSDR's use of 10 and the Dutch RIVM, which also uses 10 for that factor.

All three groups use an uncertainty factor of 3 LOAEL to NOAEL based on the minimal effects as described on EPA's IRIS and elsewhere. And only EPA uses a threefold for lack of database. ATSDR does not use that factor. Generally an RIVM I'm not sure what they do but they don't have it. So it really comes down to my way of thinking is the 30 is appropriate but it could be higher depending in part on whether or not we use this -- or need the database

uncertainty factor of 3 that EPA has put down. And so I would really like to hear Dr. Griffin's thoughts on that.

You had alluded to some other studies that I was not totally aware of, so could you help me understand, please? Or the rest of us?

DR. GRIFFIN: Okay. Well, as mentioned earlier, when we look at the database uncertainty factor, we typically apply a default of 10 if there are no reproductive or developmental studies.

Now, at the time this RfC was developed I think the reproductive studies were a bit iffy. But since that time there have been a number of studies. For example, you have the reproductive study in Davis et al., the developmental study in Morgan et al., and then a neurodevelopmental study by Herr et al., all looking at doses almost 1,000 times higher than what occupational workers would be exposed to. And either no effects were seen or effects consistent with maternal toxicity were seen.

So at levels that were much, much higher than occupational studies where we're seeing neurological effects, we are not seeing reproductive and developmental effects. So this would add weight to having less than a 10-fold uncertainty factor for that database uncertainty factor, suggesting 3 would be appropriate.

I just sort of would like to echo something that Dr. Farland said in his paper in that application of uncertainty factors to these critical effect levels, they are a, sort of, combination of science and policy. And it's very difficult to sit

back from the outside and understand what went on between internal and external reviewers when they're putting together these uncertainty factors. So I would just caution people to keep that in mind when they're, sort of, looking at something from the side and thinking, "Oh, I could do a better job of that."

DR. DOURSON: Okay, so my question to you, Dr. Griffin, is are you comfortable with the threefold uncertainty factor for within human variability in EPA's RfC given that ATSDR and RIVM use 10, as a default?

DR. GRIFFIN: You know, that's a very good question. And you know, rather than give a direct answer to that I would say that there are a lot of studies that have been conducted since this time: the Bellinger study, the DeRouen study, the Ranchian (ph.) study, the New Zealand work. FDA may want to consider reevaluating on their own this RfC in the context of all that new data and coming to their own conclusions as to what an appropriate reference level would be.

DR. DOURSON: Okay. Thank you. And that's actually consistent with Dr. Bates' and Dr. Aschner's idea of integrating more of the new data since the time of the evaluation, thank you.

DR. JEFFCOAT: Right. That's where --

Do we have consensus on that, that we should look to closer to now? So what we have consensus on is while no effects were seen in the older studies, we really need -- we need to ask the Agency to look at -- to review the newer studies to make sure that the numbers are consistent? Yes.

DR. BATES: Michael Bates. If I could just add to that? Also, not just review the REL but also review the method used, you know, because if we're going to use potentially continuous data, it will require a different method. So not just to be maybe stuck on the RfC or REL.

DR. JEFFCOAT: Well, we -- yeah. So really we're asking to look at all of it: the REL, RfC -- I mean, because there's no way to do it without doing that, and the method for the newer studies since review was conducted? Okay. Yeah.

DR. ZELIKOFF: Excuse me?

DR. JEFFCOAT: Yes, Judith.

DR. ZELIKOFF: Yeah, can the Panel again remind how we're taking the sensitive subpopulations into account in this? I haven't heard any of that and I don't think we are and I think for that reason it's not -- clearly FDA needs to take a second look at new literature, but they also need to really consider the sensitive subpopulations that I would define as pregnant women and the fetus, as well as elderly and anyone with pre-existing disease. I don't see where this is being taken into account.

DR. JEFFCOAT: Okay, well we did take it into account for looking at estimating daily doses of mercury vapor, okay. So we could simply say you apply similar models. And some of those models are going to -- they're going to be singular, they're going to -- you know, can't divide by zero, they're doing to be, you know, singular matrices, so you can't do it. And that's fine because

there's no data there. I mean, it's not fine that there's no data, but if there's no data, there's no data.

DR. DOURSON: Right. And Michael Dourson here. And in addition to that it's the use of uncertainty factors. So your uncertainty factor -- EPA's uncertainty factor of 3 for database is specifically when you're missing studies on sensitive individual groups. Developmental toxicity is in utero exposure; that's the fetus. EPA likes to see two of those studies, in different animal species, you know, not both rodents for the reason of thalidomide, and they like to see a second -- a two-generation rat reproductive study which is the only study in the suite to test rat babies and rat teen -- well, rat children.

DR. ZELIKOFF: Teenagers.

DR. DOURSON: Sorry. The teenage rats always get tested because that's when you start most of your tox studies. So if you're missing all three of those studies you tend to use like a 10-fold database factor. And there's at least one publication that supports that general use of the 10. And now that we have several studies then the use of 3 is by default accepted. You can always replace this with data. If you had data suggesting otherwise you would use the data.

In the case of within human variability, the common default is 10. You've got a human study that shows in this case a low observed adverse effect level that's minimal, threefold of that factor takes it down to the expected no observed adverse effect level, and the rest of the factor takes it down to the no

observed adverse effect level expected in sensitive individuals.

The difference between EPA's uncertainty factor of 30 includes only 3 for that adjustment. ATSDR and RIVM use a full 10. Richardson used a full 10. California uses, sort of, an unconventional 30. But the point is other people have used more and that's an arguable point. But that's where it gets accounted for. And the fact that FDA has requested maybe to look at all these new data makes a lot of sense because you may end up picking a study on the basis of sensitive individuals and then you don't need any uncertainty factor, perhaps.

DR. JEFFCOAT: All right. Okay, yes.

DR. KOTAGAL: Suresh Kotagal. I know we were talking about reference exposure levels, but sometimes that's inseparable, say, from effect. Particularly say -- if we were to look at, say, toxicogenomics, for example, looking at what genes, certain genes are up regulate, what are down regulated or -- whether it's genes or proteins, but I wonder whether that would be a more sensitive approach to determining a reference level? Because that change would occur much before a clinical change, so to speak.

DR. JEFFCOAT: Yes, why don't you go ahead and --

DR. DOURSON: Okay, so this is a really interesting question and we're now starting incororprate genomics into risk interpretation. And the expectation was that genomics would occur much lower does. But at least in the few examples we've seen is that genomic -- the cell turns on and does homeostatic things in the genomes -- sorry, I don't know the terms -- when there

are in the same doses as no observed adverse effect levels. And then when you start to get damage the genome turns on and its repair genes -- in other words, the cell says, “Hey, I’ve got damage. I need to repair,” and so it up regulates the repair genes. And then when you get extensive damage at much higher doses you get the genome to turn on and say, “Hey, apoptosis. I'm damaged beyond repair. I’ve go to,” you know, “I'm going down. I'm going to,” you know, cell suicide. And so you do see these markers. But a lot more of that needs to be done and integrated into the standard. Histopathology NOAEL, LOAEL, you know, more severe effect.

That’s a great question and we’re not just touching upon it.

DR. JEFFCOAT: But are we ready? And I will -- I just want to -- are we ready to put that in a consensus statement to the FDA at this point? Which genes?

DR. DOURSON: If you could, if you had genomic information --

DR. JEFFCOAT: Yeah, I mean --

DR. DOURSON: -- on mercury vapor exposure I think you can tie it into the more traditional histopathology and biochemistry to see how it links. That would be very important to do if you had it.

DR. KOTAGAL: Sure. So, you know, mitochondrial gene, number one. Number two, and I don't know too much about it, but certainly if we’re talking about the glutathione or selenium related genes, I think that -- I mean, if that’s -- those are the gauge, so to speak, of organ damage. So perhaps one

could look at that.

DR. JEFFCOAT: Yes. There was -- Dr. Bates?

DR. BATES: I have a question that's been puzzling me right throughout this process and this may be a question for the FDA, but it relates to this -- as we've learned yesterday that it doesn't matter, you know, where we set the REL, RfC, some people -- some substantial proportion of people are likely to exceed it in terms of the dental amalgams. So what difference does it actually make whether we raise it or lower it or change it in any way? What regulatory action potentially could flow from that because it just seems like we're -- at this stage to me seems like we're changing a number and, you know, it's just a number and it officially changed and but does anything happen as a result of that?

DR. JEFFCOAT: I think FDA probably ought to answer a regulatory question but we're not here to answer regulatory questions ourselves.

MR. WATSON: This is Anthony Watson. Changing the REL, I know it may seem like it's just a -- sort of an administrative maneuver considering that the population -- a large population may still exceed it, but I think it's important to get a consensus view of that.

We are being asked to make judgment calls and that information people rely on, as many people here have stated, have relied on FDA to come to some decision. It's important to see what the experts out there think outside of FDA when we're making these decisions.

It is not really just an exercise in number manipulation. It truly is to see what the best answer is. And so we do want to hear what people have to say about that because we have to make some decisions around that. Maybe people will -- maybe the numbers will still be above that but we do want to know what the general expert opinion is on that.

DR. JEFFCOAT: Yes, Dr. Griffin and then I want to try for a consensus statement.

DR. GRIFFIN: Yesterday, Dr. Farland in his talk mentioned the margin exposure approach. This is one example of a way to get around "Is this value better from EPA?" or "Is this value better from Cal EPA?" or "Is this value better from ATSDR?" So that's something that FDA may want to consider rather than dancing around with all the other agency's reference values.

DR. JEFFCOAT: Thank you. That's a very -- thank you for --

May I try for a consensus? People ready to --

We are suggesting that the methods from the newer studies and the data from the newer studies be reviewed in order to determine RfCs, because the question had to do with RfCs. Use an uncertainty factor when we do not have data for sensitive populations, because you have no choice, frankly. And when you do have data for sensitive populations use a model similar to the kind of models that we talked about for the RELs to get an RfC for the sensitive populations. And if it's available, analyze genomic information, such as we have it. Is that acceptable? I -- is that acceptable?

MR. WATSON: Yes. Yes.

DR. JEFFCOAT: Okay. And I'm Marjorie Jeffcoat. Olga's reminding me I don't do my name. I keep trying to remember to do yours.

Okay, all right, we're on Question 2 of the reference exposure levels.

DR. GOERING: Peter Goering, FDA. Madam Chairman, I'm -- after our helpful discussion here, I'm -- want to ask you and maybe the Panel's opinion of whether we have already covered Question Number 2 and even possibly Question Number 3. I suggest I just read a portion of each of those and maybe we could dispense with them. I think we have heard a considerable amount of information from the Panel.

So the Question Number 2, we thought this was an important issue and Dr. Richardson provided some provocative information and so we thought it needed addressing. So the second question is just basically at the bottom: Discuss the selection of uncertainty factors to derive a reference exposure level or reference concentration for mercury vapor inhalation. Provide the rationale for a selection of the most appropriate uncertainty factors. I think we have discussed that but I just want to get your approval, first.

DR. JEFFCOAT: Do we have consensus? We don't take votes. Do we have a consensus that we've handled that? Yes, sir. Is that acceptable to FDA, since FDA proposed it? All right.

DR. GOERING: So the third question, basically we wanted to

utilize the information that the expert consultants brought to you yesterday and they also discussed the RELs and how they were derived and our question was: Based on your review of this information and the discussions you have heard which, if any, of these RELs does the Panel recommend for FDA to use and why? And I think we've heard considerable discussion about using those RELs or another approach, so I'll ask.

DR. DOURSON: Okay, so what I would like to do is add to that. Michael Dourson here.

DR. JEFFCOAT: Dr. Dourson.

DR. DOURSON: So FDA has some of the best risk assessment experts in the world. The Lehman Award of the Society of Toxicology is named after one of your pioneers and you have scientists that have won the Lehman award, of course, and you have one recently that won the Society of Risk Analysis Practitioner of the Year award just last month, actually just this month. But the point is you've got the best experts in the world.

When I listen to all of the information from the last couple days, nearly all of it seems relevant to me. So that means the 150 years of amalgam implants and then the individual comments we've heard from our other colleagues and the public observers, they all seem relevant to me. And as a risk person I find them to be accepting -- I can accept all of this; not without some critique, but there's a disparity here and I have to ask myself, well, why is there this disparity?

I believe the key to this goes to what several people have said, there's this know mode of action for mercury, at least in part, where mercury can come in and bind phils, it can use up glutathione, it can do many of these things. And the disparity between practice with no effects, and we some studies about that, and yet maybe some applications where we have effects might reflect a couple things: that there is no threshold and we just can't measure it in the low dose regions, or there is a threshold and we're just observing some people are below it or some people are above it.

So from the point of view of this is idea of threshold, it might be that we are near the point of a population threshold. So some people with lots of amalgams are over it and some people with lesser are less than that.

So what I would like to enjoin, and you've already heard -- everyone is doing this, is to ask our FDA scientists, who are really very good at this, to look at these new data, the data since 1995, and really kind of develop your own reference concentration. If the critical effect is neurological, so be it. If we can use a human NOAEL from these children's studies, that would be great, but Dr. Aschner and Dr. Bates are talking about making sure that that's sufficient length of exposure. You may need an uncertainty factor there.

And by all means, use all the new tools we have in risk assessment, benchmark doses and concentrations. We can take this study on audio effects, which is a scatter plot, and we can benchmark dose set and confirm whether six amalgams is the threshold that these authors talk about.

And I heard six amalgams yesterday by somebody else. So we can benchmark those set.

We can do chemical specific adjustment factors. That's the sort of taking the actual data and replacing the default uncertainty factors of 10. You know, we can do that as well.

The physiologically based pharmacokinetic model, boy, it would be nice if someone could do that. I know there's a lot of data there. We may not be able to do it, but if we could incorporate that, maybe piggy-backing on some of the methylmercury work that has been done, that would be great.

And then finally just to compare it to methylmercury's reference dose because surprisingly these RfDs and RfCs are actually very close. So somehow we have to tie that into, you know, what we've already established for methylmercury.

DR. JEFFCOAT: Okay. Yes.

MS. DE LUCA: I think when it comes down to it, risk assessment's going to be pretty much all.

I would like to ask the FDA, and indeed information from the Panel, to come up with a more simplified risk assessment in layman's terms so that patients could actually take a look at it and say, "Ah, this is what they're talking about." You know, it's great to talk about NOAELs and LOAELs, but if we're looking in the audience, how many people are going to be on the same page? And I think that a lot of people are going to be looking for this

information and I think it would be really, really helpful to have something, even if it's in paragraph form, not in a chart form -- though I like chart forms. I think they're clear, easy to read, and make it certainly more simplified than this chart, because people aren't going to be comparing slides, but make something that let's people feel that into a risk assessment and finding out where they might be. Is that possible?

DR. GOERING: Yes.

MS. DE LUCA: Thank you.

DR. GOERING: We have communications experts that can help us put what we do in lay language.

DR. JEFFCOAT: But this needs to be done first so you know what you want to communicate. This is Marjorie Jeffcoat. Of course -- I know it's obvious but just for the record.

MS. DE LUCA: But you couldn't put it later at another time because then there would no tangential relationship.

DR. JEFFCOAT: Yes.

DR. BURBACHER: Actually, I'd like to, I guess, discuss a little bit on -- based on your comments. I mean, they're -- if you do this and it's not transparent and it's not something that the community can follow all along, you're just going to come up with another risk assessment that nobody's going to believe. So, I mean, I think this whole process needs to be very transparent. It has to be, you know, open to the community as much as possible in terms of

how decisions are being made as you go along the line.

So I wouldn't agree that, you know, you can't -- that you can't bring the community in until you're finished. I mean, I think one thing we've learned from a lot of these processes is that if you don't bring them in early and have them, you know, have them know what's going on, what kind of decisions are made and what's the basis of those decisions, when you get finished it's not going to worth anything. And you're going to - you'll be basically where you were from the beginning in terms of, you know, the integrity and how people would believe what you did.

So I mean, that's a process that's going on in a lot of different agencies now in terms of being open and transparent.

DR. JEFFCOAT: I think though we're talking about two different stages. I'm talking about what -- as the data crunching is going on the data crunching needs people who do data crunching. And then you need to get involved people who are trying to figure out, well, what do you do with this information now that you have it? And what more information do you need? That's part of what this Panel's doing. That's why we have different representatives on this Panel.

DR. BURBACHER: Yeah, I mean, it may be a minor point but I'm just saying that --

DR. JEFFCOAT: Yeah.

DR. BURBACHER: -- while the data crunching is going on there

needs to be some communication about what data crunching's going on and why the data were chosen. You know, those kinds of issues.

DR. JEFFCOAT: Okay. So are -- yes, I'm sorry, you did say you wanted to --

DR. WHITE: Joel White.

DR. JEFFCOAT: Yes, Joel, I'm sorry.

DR. WHITE: I'm not good with my name but I'm getting better at it. Just I want to echo what I heard here. Having not been immersed in risk assessment, only tangentially knowledgeable about it, I've learned a lot about it in this Panel meeting and in preparation. It seems to me, and I want to echo, that LOAELs are very close amongst the four studies. So if FDA were to do one thing it would be batten down the uncertainty factors with the new data.

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

DR. JEFFCOAT: Yes.

DR. FLEMING: Yeah, Michael Fleming here.

DR. JEFFCOAT: Dr. Fleming.

DR. FLEMING: Let me see, I want to make sure I understand that we are not, as a Panel, necessarily endorsing the EPA RfC; is that correct?

DR. JEFFCOAT: No.

DR. FLEMING: We're just simply saying that we don't have enough data to know what it should be? Yeah, I want -- I know it's a very simplistic question --

DR. JEFFCOAT: That's what we said.

DR. FLEMING: -- but I want to make sure that I do understand that we're not endorsing --

DR. JEFFCOAT: That's what --

DR. FLEMING: -- the use of that REL?

DR. JEFFCOAT: That's what we said, right. And we said go back to the newer -- see if there's something more there. Yes, ma'am.

MS. RUE: Karen Rue. And I know it's a little down the road but with everybody talking about getting information to the consumer, I would like to suggest that it's done in collaboration with all the dental societies because as wonderful as the FDA website it, that's not where people go to get their information; it's within the dental offices and where they receive the service.

DR. JEFFCOAT: You're right. I think.

Okay. Does FDA have the information they need for this or --

MR. WATSON: Yeah, this discussion was helpful.

DR. JEFFCOAT: Okay, good. One addition.

DR. DOURSON: Just one addition on this communication model.

DR. JEFFCOAT: Okay.

DR. DOURSON: I really like this idea of communication and it occurred to me thinking about that and what Dr. Griffin said, there is a communication model for biological equivalents published by Sean Hays and his colleagues, where they step through and give this idea of margin of exposure, point of departure, this supposed bright line, and lays it all out, and Health Canada is now picking this up, as well as -- in their communications. So I can give you some information on that. You may have already read the Hays et al. paper. I'll transmit that information through the Chair to you gentle folks.

DR. JEFFCOAT: Thank you. Then I'll have it and can read it.

Okay, FDA, the chair is yours. I mean, the -- yeah. Not the chair. We're on to Number 3.

DR. GOERING: Okay, the final series of questions relates to the clinical study database.

In FDA's final rule, FDA stated that human clinical studies of dental amalgam bearers have not established a causal link between dental amalgam and adverse health effects in adults and children age 6 and older. This conclusion relied on many human clinical studies reviewed in the FDA White Paper, Addendum and final rule. FDA stated in its rule that human clinical data for children under the age of 6 and pregnant women, including exposures to the

fetus, is limited. The petitioners dispute the methodology, conclusions, and FDA's interpretation of these studies.

So the two questions in this section are -- or comments for discussion are: Assess the strengths and the weaknesses of the clinical studies on dental amalgam, including whether appropriate endpoints were evaluated.

Number 2: Do the clinical studies support a relationship between exposure to mercury vapor released from dental amalgam and adverse health effects associated with renal, immunological, allergic, neurobehavioral or psychological function? Are there other adverse health events identified by these clinical studies?

DR. JEFFCOAT: Now is the time for the outcomes. Everybody's been waiting. And I believe Dr. Tinanoff was the first up.

DR. TINANOFF: We have spent 2 days talking about the risks of dental amalgam. And there are endpoints that we really haven't looked at and clinical endpoints and that is the other side of it, what are the benefits? And there are studies, especially the Casa Pia study, that looks at the benefits of amalgam and compares that to the benefits of composite. And I think that's really critical as we are evaluating the risks versus the benefits.

So I did a little reanalysis of the Casa Pia study looking at amalgam survival and composite survival, and from my calculation the amalgam survival was 10% better than the composite. So the benefits of amalgam is it's better and, from their conclusion also, that the failures on composite were multi-

surface restorations. So the benefit of amalgam is it's better on multi-surface restorations and it's less technique sensitive. And in conclusion, this endpoint -- actually, I think it's very important, is the benefit and that's about a 10% benefit when you're comparing amalgam to composite restorations.

I know it's off topic but I think it's very important to recognize that.

DR. JEFFCOAT: Actually, it's not off topic, I don't think. But maybe that's -- okay. Yes, I know you've been -- you have the floor.

DR. KOTAGAL: Thank you. I'm just checking my comments to III --

DR. JEFFCOAT: Dr. Kotagal, for the record.

DR. KOTAGAL: Suresh Kotagal. With regard, you know, Section III issue, number 1, and my comments are mainly about the Casa Pia study, the DeRouen study that was published in *JAMA*. So I have some questions about the methodology.

First of all, they have used a comprehensive test of non-verbal intelligence to measure the effects. And that's the kind of test one would use, say, for a hearing impaired child. The normal values, the reference values in the United States for children are 100. At baseline their -- both the groups had values around 85 and 7 years later the values were 81, probably was not powered enough. So anyways, so that was one test they used. My question is, is that a valid or appropriate test? I'm not a neuropsychologist but I would question that.

Then the second issue is that they used the Wechsler abbreviated scale of intelligence, not a baseline, only at year 7, so we don't have baseline information about it. The Wechsler abbreviated scale of intelligence is derived from the Wechsler adult intelligence scale. It's an adult -- a section of the WAIS, which is an adult instrument. So there was no baseline for it and they used an adult scale.

Third issue I mentioned briefly yesterday, too, they measured motonerve conduction velocities and we're hearing about hearing loss, glove-and-stocking, as they said, you know, years and years ago in other studies. So mercury is more prone to cause a sensory neuropathy. There were no tests of sensory nerve conduction so I have concerns about the validity of these tests.

The other issue is the children were 8 to 10 years of age, past the critical steps in neurodevelopment, which -- you know, malinations and apogenesis, they're going on very rapidly in the first 3 to 4 or 5, 6 years of life. So these kids are really older by which point we may not have seen, or at least in this short period of time, any adverse effects. So I really feel that we don't have any adequate neuropsychological information in preadolescent children there that we can rely on.

DR. JEFFCOAT: Thank you, that was very clear.

MS. DE LUCA: Madam Chairman?

DR. JEFFCOAT: Yes? Ah, there you are. Okay.

MS. DE LUCA: Just a comment and it may be peripheral but it may

also be germane. I think that probably the reason that they chose the California and the modified version -- I was a reading specialist, taught elementary right through high school -- is that you can keep going and look through the records. So it's something easily available. You don't have to readjust, do new testing, which I think in your office is optimal. But I think probably for the general dentist is not going to be optimal; they're not going to want to administer tests, but they could get that from the school information by sending a note. So that's probably, I think, a good idea and maybe where that comes from.

But I think in terms of really specialized populations and people with disabilities such as you were mentioning, that's a special population and they need to be cared for exactly because they don't respond to the California in verbal ways that need to be accounted for.

DR. JEFFCOAT: Yes.

MS. RUE: Karen Rue.

DR. JEFFCOAT: Ms. Rue.

MS. RUE: I just want to say with the FDA, they've always been there to establish the safety or evaluate the safety and the efficacy of different products and the efficacy obviously has been established, but I feel that the safety issue from everything we've heard in the last 2 days still is in question. And especially when there are quite a few alternatives available. Thank you.

DR. JEFFCOAT: Dr. Bui.

DR. BUI: Yes, I just have a comment and probably a suggestion for

the FDA. At the recent -- meeting for Avastin's breast cancer indications, the Committee discussed quite a bit one endpoint they want to look at is quality of life. And from the industry standard now is for almost every oncology clinical trial that's something we consider as one of the end point, quality of life. So that's something I would suggest to the FDA in terms of looking at a clinical trial, that you might to consider quality of life as one of the endpoint, whether it's primary or secondary endpoint.

DR. JEFFCOAT: Yes.

DR. FLEMING: Yeah, Michael Fleming here. I wanted to echo what our Consumer Rep said here, that very often -- 4 years ago we -- I had the privilege of serving on the Panel on this matter and one of the things that seemed to get mixed up a little bit was the difference between safety and efficacy. It's very easy, I think to -- well, efficacy is -- I don't think anyone debates much about the effectiveness of amalgam, and perhaps some of the limitations of our composites. I -- you know, my concern is the risk. And I'm not even sure that what we're doing is a risk-benefit analysis. I think risk is a standalone issue, aside from benefits and effectiveness. So I do echo that concern that we focus on that part of it.

DR. JEFFCOAT: Yes, Dr. Bates.

DR. BATES: Thank you. I interpret the part of the question that asks about whether appropriate endpoints are evaluated, as an opportunity to identify gaps in the available data; is that reasonable? And I think there are

quite a few. We do tend, I think, to wait for people in the academic community to do studies and then they appear as before this committee or -- but I think it's also important to call for -- you know, identify specifically particular endpoints and call for further studies to be done. And I would in that regard particularly like to mention the neurodegenerative diseases, MS, Alzheimer's and Parkinson's.

DR. JEFFCOAT: Um-hum.

DR. BATES: We've heard various opinions yesterday from speakers, but having reviewed the literature myself, I can say that the data on these three outcomes are very inadequate and really one couldn't make any judgment whatsoever. And so I think it would be appropriate for this committee recommend that more studies be done. And I think actually that it goes to the FDA position. They have mentioned that there's a paucity of such studies but it wouldn't hurt for this committee to actually reinforce that, so maybe independent investigators out there will perhaps carry out some such studies.

DR. JEFFCOAT: If the Panel doesn't feel it's inappropriate I would like to raise a point, which is fillings, whatever kind of fillings they are -- that's why I said fillings -- are done for a reason; the patient has dental caries, presumably. Dental caries is a chronic disease and it's an infectious disease. Could you not interpret the data that the infectious disease is associated with all these outcomes, these adverse outcomes? I'm not saying it is; I'm just saying, "I don't know from these data." I can't say which it is. Because to need six new

fillings during a time of a pregnancy, that's very rampant in caries. Something else is going on. I see a lot of pregnant women.

DR. ANUSAVICE: Maybe a little bit off-target, but in reviewing the literature, my concerns stem with different socioeconomic statuses worldwide, not just in the U.S. For example, public health opportunities are given to Scandinavian children from virtually birth until age 18 and so when those data are pooled together with some of the other data, whether we're talking about adult Swedes or adult Scandinavians in general, those are confounding factors, and I haven't heard any of that come out here in terms of, you know, whether these populations should be collated or whether they should be isolated according to public health measures in those areas of the world. How do we analyze this? So I need a data miner to know how we should collectively look at the data.

DR. JEFFCOAT: You need a lot of it.

DR. ANUSAVICE: We've heard a scattering of it during the last 2 days and it's just mind boggling to try to integrate any of this into a cohesive mass and this is what we're going to leave you with when we go home tonight, so is there anyone that can kind of offer some help here how to -- are we dealing with U.S., are we dealing with worldwide populations, that would be the first question I'd ask. Since you are a U.S. agency, maybe the FDA can answer how you prioritize worldwide data versus U.S. data.

MR. WATSON: This is Anthony Watson. I'm going to defer here

to Peter in a minute. I just want to say we are interested in the U.S. population. So I mean, there's a lot of information out there about, you know, WHO, and some other information around other populations that deal with worldwide issues, but we are focusing primarily on the U.S. population here, but I'll also hand it over to Peter.

DR. GOERING: I don't think I have a good answer for your question. I think the agency is tasked with protecting the health of the U.S. population, primarily. I don't think we are disinterested in global populations. I think that data from studies from other countries are adequate for us to consider. I don't know if that was what you were referring to or not, but I don't have a good answer for your question.

DR. ANUSAVICE: Well, I think it was more related to the measuring tools, the variables we've been discussing, number of surfaces, area and all this. The philosophy of treatment is different from one part of the world to another, so you're going to see some pretty large differences in that regard and who's going to filter these out? Are we going to identify where the limit should be and maybe --

DR. ISMAIL: Well, I mean -- this is Amid. May I? Dr. Jeffcoat --

DR. JEFFCOAT: Yes.

DR. ISMAIL: -- may I speak?

DR. JEFFCOAT: You may.

DR. ISMAIL: Thank you. Amid Ismail. This is a valid point.

However, there is -- I think we should go back to the important question: Is amalgam safe? And the best human studies -- and epidemiology has been hit hard during the last 2 days. Epidemiology has been used to -- HIV. You have all the major -- tobacco is mostly epidemiological studies before even the basic science study started. The safety of amalgam, there are more recent studies even in addition to the studies done by the University of Washington and New England study and so on. There are additional studies. There's a large Canadian study, cohort study, which is the best evidence to assess harm in populations.

I suggest an independent body, which is the AHRQ, the Agency for Healthcare Research and Quality, evidence practice centers -- I think there are now 15 or 13 of them -- to do a systematic review on the safety of amalgam using clinical studies -- of course, that's what they do; they don't look at animal studies; they just look at clinical studies -- using the standards of evidence that's used in systematic reviews to come with a summary and maybe a meta-analysis of all the data to reach a conclusion on -- to answer the question, is amalgam safe in different population groups, in different ages, in males or females, different, maybe, sensitivities or susceptible populations, if there are data on those. And that would be a definitive review that could be used by the FDA.

DR. JEFFCOAT: Other comments?

Yes, Dr. Dourson.

DR. DOURSON: Mike Dourson. Just to add a little bit to that comment. I liked it very much. I'd like the idea of perhaps not just saying is use safe but perhaps -- and this probably will come up -- is some point at which the use is not safe? Because, after all, as a toxicologist, we're trained in this idea of thresholds. At some point, because we know or we think we know the mechanism or mode of action of mercury, we know that your body can take some of it on. After all, if we use up our glutathione, we up-regulate and make more. So there is this idea of threshold or not and perhaps we've exceeded it.

Another technique is categorical regression that we use with animal mixed-dot data, animal toxicology and epidemiology data. It's another way to do meta-analysis, but you can throw in the animal data. It's probably not as good as what you're recommending, however.

So thank you.

DR. JEFFCOAT: Other questions?

It looks like Van is thinking about saying something.

DR. THOMPSON: Two things.

DR. JEFFCOAT: Dr. Thompson.

DR. THOMPSON: First of all, addressing Dr. Anusavice's question about where we were these days, different areas of the world and so forth. And one of the studies that's recently come out, published online with the *Journal of Dental Research*, is the Opdam study, looking at large

three, four, and five-surface amalgams in composite -- and this goes to Norm Tinanoff, too -- in high, medium, and low-risk populations for caries.

And in essence, what they were showing was that large composites held up very well in the low and medium-risk patients. Only in high-risk was there a difference, but by the end of the 12 years over this study, the difference was very, very small. Failure reasons were different.

But in essence, it said the large restorations were holding up quite well. So there were -- let's call them equivalent, at least, if not better, for the composite. So that's some new data that we haven't had that's much more recent.

I think the other thing is we have the concern -- I would like to see the studies done as proposed, and the summary, done as suggested by Amid Ismail, but I think that the concern that I have is we still have what is identified for us, a number of people that are a sensitive population, and what data can we glean from them, perhaps, about what are threshold levels for them?

A number of people have talked about okay, we've been detoxified to some extent. Okay, what is your mercury level now? If that is where you have some recovery, what is it? Because there is a load there and I'd like to know what that is to just get some idea. Ad so I think we have an identified group that we could learn something from and work with to find out. We don't know necessarily all the causes, but we have some idea what's

at level.

DR. JEFFCOAT: Yes.

DR. WHITE: Joel White again. We're off-topic but since we're going that way, we're kind of getting to the end.

DR. JEFFCOAT: I'm going to bring us towards the topic in a minute.

DR. WHITE: Thank you. I want to just --

DR. JEFFCOAT: I'll let you speak first.

DR. WHITE: Thank you.

The question before us are regarding the endpoints and the strength and the studies on dental amalgam. And having done a lot of regulatory filings with the FDA, the studies that we've seen here, the Casa Pia study and other studies brought before us, have actually been very good trials, have tried their best to take science and measure outcomes.

And as we heard from an impassioned presenter, there was a bias towards the null and so if you put the science that's there, I do not see any scientifically credible reason to recall or curtail or change the use of amalgam. I can't possibly -- we're not voting on it, but our recommendation is that, from a science perspective, there's no compelling reason to do that. But on the other hand, we have environmental issues, that's clear, and lowering mercury in the environment is a good thing. And lowering it --

DR. JEFFCOAT: I don't think we're discussing that.

DR. WHITE: But I'm just --

DR. JEFFCOAT: I don't think.

DR. WHITE: Right. So we have to kind of transition from the "no, there is no compelling science," to "can we do it better," and there's been lots of good ideas there.

And then, down on Number 3 on the list here is the statement that FDA has, what improvements can be made regarding labeling, disclosure, to help today, right now, and I have some ideas on that when we get down to it.

So the answer to Number 1, the endpoints are good, the studies were good, they did not show an effect.

Number 2, there is no causal link between these different disease states and the use of amalgam that's shown by the science. However, I'm swayed by all these compilations of case studies.

But Number 3 on the list is what do we know from all of this that can help with the labeling and the disclosure from FDA today, so I'd like to get down to that.

DR. JEFFCOAT: Okay. So let's --

MS. DE LUCA: Marjorie.

DR. JEFFCOAT: Oh, I'm sorry. You're right. You do keep getting missed. I apologize for that.

MS. DE LUCA: This is quite -- but since the door has been

opened, I would like to bring up something that really concerns me. I have seen ads in my local paper and in magazines, and I think there needs to be -- people need to understand that there are standards for detox and chelation. This is not something that you do lightly. It shouldn't be at your massage therapist's apartment. This really concerns me. That some standards and that people, general public, understands that there are standards.

DR. JEFFCOAT: Oh, okay.

MS. DE LUCA: That it's not a simple thing that anybody can do for you, like somebody with a high school diploma, or not.

DR. JEFFCOAT: Okay, Dr. Griffin. And then I'm going to try and do consensus of 1 and 2.

DR. GRIFFIN: Okay. I'm probably just restating --

DR. JEFFCOAT: That's all right.

DR. GRIFFIN: -- what people before me have said.

I think that the studies listed here provide very compelling evidence that there is no effect level that can be identified in a general population and I do think that this gives us a handle on effect levels in the general population, but I want to also echo my concerns that there does appear to be a very susceptible subpopulation to immunological effects. I had really hoped we could get into that, I know, because it was one of the questions on earlier papers. So I have a concern for that, also.

DR. JEFFCOAT: Yes, Dr. Bates.

DR. BATES: Thank you.

Before we move past Number 2, I do want to mention this paper on hearing loss that I asked to be circulated yesterday, because I think -- I'm fairly familiar with the epidemiologic literature in this area and a lot of the arguments about whether amalgam is harmful based around, say, occupational studies and trying to extrapolate the range of effects. But here we have a paper which actually shows an apparent effect based on number of amalgam fillings.

It was a small study but a particular feature of it, the authors went to a great deal of trouble to kind of focus on a particular subgroup, women, nonsmoking women, aged, I think, 40 to 45. And by being very specific, they eliminated a lot of the possibility of confounding.

Most of us would probably just have gone out and collected 100 women and then tried to do a multi-various adjustment. They went to a lot of trouble. And because they selected a very specific group, you might argue that, well, it's only -- it's not generalizable past that group and it is an isolated result.

It does need to be reconfirmed. But nonetheless, when you look at this graph here, it is -- the horizontal axis is number of amalgam fillings and threshold of hearing and it does appear with a number of amalgam fillings based on these data that there is progressive hearing loss and there's no evidence, obvious evidence, there of any sort of threshold.

Now, I'm not saying that on its own this paper should be considered, sort of, any sort of definitive evidence of amalgam harm, but nonetheless it is -- presents, sort of, a prima facie case and I do believe that other studies should be done looking at hearing loss, because this is an isolated paper. Probably nobody ever thought to look at this before.

So I do think that in our recommendation, if we're going to make recommendations, we should propose that there be other studies looking at hearing loss. I think it's quite important. Because, to me, this appears to be, you know, a reasonably strong signal, albeit an isolated paper.

DR. JEFFCOAT: I would like to ask a question of FDA. Are we supposed to make recommendations regarding other studies that would probably be in NIH's bailiwick or is that okay?

MR. WATSON: Sure. I mean, we --

DR. JEFFCOAT: I mean, there have been questions about that. I mean, you know, standard --

MR. WATSON: We want to get the best information -- I'm sorry. I'm sorry.

We want to get the best information to make our decision, so if the group thinks we ought to do that, then the answer is yes, we would like to know what you think we should be looking into.

DR. JEFFCOAT: Okay. Yes.

DR. JANOSKY: Janine Janosky. I have a question for FDA and

also for the Panel, is that is the language within III, the introduction, and within Number 2, purposeful or not? Because the introduction is talking about a causal link and Number 2 is talking about a relationship, and these are two very different concepts. And in some of the discussion within Panel, I think is not distinguishing between the two.

So my question for FDA is, is your language purposeful? So are you asking us about causal linkages as a result of these studies in our interpretation of them or are you asking us about relationships and whether we feel that there are relationships?

DR. GOERING: Peter Goering. I think our use of the two terms was not intentional. I think we were -- didn't intend to have the introduction talk about a causal link and Question Number 2 just discuss relationships. We're interested in your opinion on both, if that's possible and fruitful to discuss, but --

DR. JEFFCOAT: Yes.

DR. ISMAIL: The rules for evidence for cause -- is very hard and it was very hard with this case. However, to show that there's a probabilistic relationship that's strong, the odds of disease or risk of disease increase with certain levels of exposure and that's what I think most the studies are addressing.

The hearing study is a good start. However, they limited the sample to high level of education in the UK and only in those women with

very high level, the highest level of education.

You look at the -- where the significant relationship starts to appear is in high ranges of the stimulation, the kilohertz. It starts to appear around 11.2 to 16, but doesn't appear below it. So there is something funny there to look further into. And it's not linear, if you look at the regression coefficients. They don't increase in a dose response relationship.

So these factors raise an issue about the sample, itself, but it's an association that needs to be investigated thoroughly, as all other claims that we have and we have heard, as well.

DR. JEFFCOAT: Go right ahead.

DR. DOURSON: Mike Dourson. Just to add to that, I very much like the study on hearing loss, so I held up before -- I didn't know of these extra things. Dr. Ismail, thank you for that. You're right, it's a linear regression but, of course, it's built to be linear so of course it'll be linear. However, we could use benchmark doses with this as a way to get to some point of departure, if we do wanted to do that.

I had a question for Dr. Aschner, so just going to a different study, the Casa Pia study. You had indicated, I think, earlier that the neurological deficit of early exposure going on for 7 or 10 years, we might not be able to see that in 40 years. So that's what I think I heard you say, so it would be -- if we were to use that particular study as one basis of this collaborative or collage of studies -- and let's say that became the principal

study, do we need an uncertainty factor to address length of exposure or sensitive individual with those kind of results? Do you have any thoughts on that?

DR. ASCHNER: Well, I can't address the uncertainty factor because it's not really my domain, but I think there's plenty of evidence from different studies we've led, for example, with methylmercury, that early exposure can result in late neurodegenerative effects.

So you know, if you look at kids when they're 6 or 7, it's not going to tell you anything about -- look at a certain neurotransmitter, for example, dopamine, they might lose 30 or 50% of the content of dopamine in their brain and if you do any behavioral test, they'll be completely normal. It won't be until they lost 80 or 90% of these cells and even if they're on a trajectory for a normal decline in the number of these cells, these effects would be apparent at a much earlier age.

I don't know, I haven't heard if any of these studies have actually corrected for things like that. But whether you need -- it would seem that it would need some kind of a factor to control for the risk, but I don't know what the policy is in terms of this kind of effect.

DR. DOURSON: Thank you.

DR. JEFFCOAT: Okay. Oh, I'm sorry. Judith. And then I want to try and summarize 1 and 2 and go to the next question.

DR. ZELIKOFF: Oh, I didn't think you were doing 2 so I stayed

quiet.

DR. JEFFCOAT: No, no. We're at 1 and 2 under III. We're on Number III, Human Clinical Studies.

DR. ZELIKOFF: Okay. I'm sorry. I didn't think you were doing the immunological approaches and all. We're doing that now?

DR. JEFFCOAT: Um-hum. Because people have been doing it, so --

DR. ZELIKOFF: Okay.

DR. JEFFCOAT: -- that's why I want to try and go into --

DR. ZELIKOFF: Oh, okay. Well, my first comment wasn't related to that. It was related to the causal link and I thank you very much for bringing that up because I think that FDA really needs to reconsider that wording.

As a toxicologist, having fights with the epidemiologists usually, I really feel very strongly that establishing a causal link really needs animal studies to provide biological plausibility. I really feel that an epidemiological study -- while clear associations can be made, that to really get down to it, to causality, you have to be able to show that there's a mechanism that can be responsible for that and that that can clearly happen. We've seen that in the past with numerous environmental chemicals.

So I almost want to say that that word, maybe association should go back or just a link should go into Number III. So I'd like to make

that point.

Since we are talking about Number 2, as well, I clearly have strong comments about that. I think that there are a number -- I've heard it by some speakers, I've heard it by FDA, I've heard it from some Panel members, in terms of the low risk of -- excuse me -- metal sensitivity, in terms of allergic reaction; it's an allergic -- hypersensitivity responses. And it's not so low. I mean, I've heard it called extremely rare. I don't know how you define extremely rare, but in searching the literature, I found anything from 2% to 5% of the North American population.

The other thing to be taken into consideration is whether it's a mercury allergy or hypersensitivity and I discern the two very clearly. Allergy is a Type I hypersensitivity and II, III, and IV are not considered true atopy or allergy, so I think we need to be careful about that. But I don't think having a 2 or 5% allergy is low for the North American population.

The other thing is that although nickel -- and I'm not a dentist and I'm not a mechanic in terms of dental amalgam, but I don't think nickel is in there, at least from what I've read, and there are oftentimes some cross-reactivities and cross-sensitivities with nickel. And nickel allergies in this country, especially for women, are very -- well, are high. I've heard ranges anywhere from 13 to 30% for women. And if you go into little bling-bling shops in malls, you'll see how many women are really wearing cheap earrings and belts and everything else. So -- and men.

So the nickel allergy is something that should not be negated when thinking about allergic individuals. And clearly, the hypersensitivity reactions associated with immunological responses, clearly there's a wealth of information, at least I would call it that, in rodent models. Droy (ph.) has done a lot of work with mercury and elemental mercury in animal models, and more and more information is starting to come out.

Ellen Silbergeld had a paper where she examined people in Brazil, and I'd like to see more from her in this case, but she did notice that low -- she reported that low levels of elemental mercury in gold miners exacerbated systemic lupus erythematosus and also had some impact on scleroderma. I'd like to see a follow-up. It wasn't the most compelling paper; it was a short paper, but clearly it was there and I think that we need to really look -- FDA really needs to look into that.

I think, in terms of autoimmunity, that's something that there is more information on. It's also considering quality of life, as we've just heard from another panelist. That's something that has to be considered. Autoimmunity is not something, lupus is not something, scleroderma is not something you can take very lightly. It can destroy quality of life dramatically, so I think we need to look into that.

As far as I've also heard, and I wanted to correct what I've heard, in terms of the immunological effects of mercury not being well studied. Being a toxicologist, an animal model toxicologist, and I went

through some of the papers yesterday and did a literature search and there is quite a bit of information of mercury, clearly not as much for elemental mercury, a lot for inorganic. A lot for inorganic. And from what I understand, at least when it gets into the brain, elemental mercury is inorganic mercury. It's the same with methylmercury. And so I think we have to consider that, as well.

There are a lot of changes in terms of lymphocyte proliferation, which is linked to autoimmunity. There's activation of the lymphocytes, there's increased cytokine biological mediators that are released, pro-inflammatory cytokines that have been measured in blood as well as in animal models. So there is information out there in terms of regarding the immunological changes. Now, whether that's a point of departure or -- and now I'm just talking about immune suppression.

Changes in the immune response is going to lead to possibly increased incidents of bacterial infections, viral infections, et cetera, but is that an obvious effect right now or is it a subclinical change, so I think that's -- you know, I don't think immune suppression could be a point of departure because you're not seeing it right then and there, but as far as autoimmunity, I think the FDA needs to do a lot more work in terms of looking into that and I think it could be a very important endpoint that needs to be evaluated better.

DR. JEFFCOAT: Thank you.

Yes, Dr. Anusavice.

DR. ANUSAVICE: Thank you for the comment because it's an area -- the allergy component is what I'm referring to here, is one of these areas that's mystified me over the years, too, and the statement that was made in the last document in 2009.

I'm not aware of the allergy to amalgam being as high as 5%. The reason that there may be some confusion in what that number should be is --

DR. ZELIKOFF: I'm sorry, I said mercury.

DR. ANUSAVICE: Mercury, okay. Mercury is -- may be different.

But with amalgam, we have white lesions that are sometimes attributed to the presence of amalgam especially if the occurrence is next to the restoration site and these usually result after the amalgam is removed.

In the few cases I've actually heard about -- and I haven't read anything in the literature in the last 10 years regarding allergy, is that it's a self-limiting reaction, if there is one that occurs, where you get redness around the mouth or intra-orally. And so the old school said that if you just wait 2 weeks, this will resolve on its own and I've not seen any follow-up to these statements, whether they're still accurate in that assessment or not.

So I think there is room to clarify that aspect of it and I believe most of the intra-oral cases would be Type IV, which would be delayed, but there could be a few Type I's. I've never heard of one, but could be, so thank

you.

DR. JEFFCOAT: Yes, Dr. Fleming.

DR. FLEMING: Yes. Mike Fleming here.

I wanted to follow up with Dr. Zelikoff and perhaps remind members of the Panel who are not clinical dentists that nickel crowns, nickel -- with nickel substrates were used extensively in the 1980s and the 1990s and we still use them in dentistry, although it's being minimized.

There are nickel chromium alloy that contained beryllium in the 1980s and so if you had this in the same mouth with amalgams, it is likely that there would be more of an accelerated release of particulates and mercury, in particular, from the restorations. But I still routinely, when asked, and we need to find these crowns in patients' mouths extensively.

DR. JEFFCOAT: Okay, yes.

DR. KOTAGAL: Suresh Kotagal.

Just a quick follow-up with regard to the comment by Dr. Dourson and Dr. Aschner.

You know, there's exposure and there's a long latent period before one becomes clinically symptomatic. So really, there is a synaptic redundancy in the system. We can lose a bunch of synapses but not really have function affected and for example, you know, senile clogs develop in our brain starting around 25, 26 years of age.

Mild cognitive impairment doesn't occurs until the fifties or

sixties and maybe a decade later, so there is really a period where there is silently things are going wrong, but we are just not aware.

DR. JEFFCOAT: Okay, let's take Numbers 1 and 2 and see where we stand. Okay? 1 and 2 under Roman numeral III: Assessing the strengths and weaknesses of the clinical studies on dental amalgam -- and I think we've gone over that quite well, for the size of the trials. They're good trials but they don't address everything as -- I don't know any trial that does, personally. That was an editorial comment. Strike that from the record.

And they were appropriate endpoints, but they may not be the newest endpoints to look at, for example, as Dr. Kotagal was explaining, the neurological endpoints that might have been able to be used but would be perhaps difficult to use in a big population of -- and most studies, many of those studies, were in children.

These studies were not designed to determine which came first, the chicken or the egg. It's the diseases associated, and I'm saying associated, not caused, because we said we're not going to do causative, associated with either the carious disease or is it associated with the amalgam itself, the restoration. They weren't designed to do that and, frankly, you'd have to use -- I think you'd have to use your desk, Dr. Kotagal, to do that, but that's -- does anyone have anything they want to add to Roman Numeral III, Number 1? Yeah, sure.

DR. BURBACHER: A minor comment --

DR. JEFFCOAT: Sure.

DR. BURBACHER: -- is that they're all -- I don't think they were all appropriate and I think it was mentioned before that to use the WAIS on 7-year-old kids is kind of strange.

DR. JEFFCOAT: To use the what?

DR. BURBACHER: The W-A-I-S. It's the Wechsler Adult Intelligence Scale.

DR. JEFFCOAT: Oh, yes. Yeah. That -- I'm sorry. Yeah.

DR. BURBACHER: That seems to have been --

DR. JEFFCOAT: That's why I mentioned the -- yeah.

DR. BURBACHER: Well, you mentioned that they were appropriate.

DR. JEFFCOAT: Yeah, I'm sorry. Yes.

DR. BURBACHER: At least --

DR. JEFFCOAT: Yeah, that's -- you're quite right. Okay. Mostly all appropriate. Right.

Okay. Do the clinical studies support a relationship between exposure to mercury vapor released from dental amalgam, okay, and adverse health events associated with renal -- and I don't need to do the laundry list again.

Are there other adverse health events identified by these clinical studies? These clinical studies really didn't answer this question very

much. I mean, these clinical studies say that in the population as a whole, it looks good. But they did not really get at who might be or identifying who might be the susceptible subpopulation.

And Norm has -- Dr. Tinanoff --

DR. TINANOFF: I think the word in there should be --

DR. JEFFCOAT: Sensitive?

DR. TINANOFF: That some of these tests weren't sensitive enough --

DR. JEFFCOAT: Yeah.

DR. TINANOFF: -- to detect differences.

DR. JEFFCOAT: And frankly, to do all this, you need a lot of people and I think everyone sitting around this table realizes that.

Yes, Dr. Aschner.

DR. ASCHNER: Is it true that all these studies were negative? My recollection of some of the Echevarria studies and Woods studies is that they did find things.

DR. JEFFCOAT: They found effects.

DR. ASCHNER: Well, if we look at --

DR. JEFFCOAT: Yeah.

DR. ASCHNER: -- expression of different enzymes in urine.

DR. JEFFCOAT: Okay.

DR. ASCHNER: To me, that's a biomarker of effect.

DR. JEFFCOAT: All right, all right.

I guess I was going for what was being discussed mostly around this table, which was do we see an actual neurological effect but not necessarily a genetic one, because that's where I said we were going --

DR. ASCHNER: I don't think we can answer the question because --

DR. JEFFCOAT: Yeah, I --

DR. ASCHNER: -- we're going around because we said that the right tests have not been performed --

DR. JEFFCOAT: Yeah.

DR. ASCHNER: -- so they didn't see any neurological effects in most cases, but the question is, were the right neurological tests performed --

DR. JEFFCOAT: Well, that's --

DR. ASCHNER: -- at the right time.

DR. JEFFCOAT: I think that's what --

DR. DOURSON: Yeah, Mike Dourson here and this paper by Rothwell and Boyd that Dr. Bates referred to before, that's not a clinical study. It is a clinical study, so --

DR. JEFFCOAT: Yeah.

DR. DOURSON: -- I mean, there are some issues with it that Dr. Ismail had talked about, but it certainly is suggestive, right?

DR. JEFFCOAT: Um-hum. Yes.

DR. ISMAIL: However, if you include the Rothwell study, you have to include the other clinical studies and I think what we need to do before we make a statement is to go and look at all the new clinical studies that are coming out. The Canadian study, Dr. Bates' study, you have 20,000 people who have been followed.

DR. BATES: That was published a few years ago. We'd just like to extend it, extend the follow-up. So it's not done, not funded yet.

DR. ISMAIL: But it's published study that we have to include in the docket for all clinical studies that looked at effects in populations.

DR. BATES: It was published in 2004, so I don't know whether it would be --

DR. JEFFCOAT: It should be --

DR. BATES: I don't think it's -- it was in the White Paper --

DR. JEFFCOAT: Yeah.

DR. BATES: -- that was, you know, for the 2006 meeting. It's mentioned there.

DR. DOURSON: Yeah, Dr. Ismail --

DR. BATES: And no way want to not support what you're suggesting. I think it's a great idea, that multiple regression analysis of the clinical studies would be a great idea. I was just going to that specific question. It looks like there are some studies, as Dr. Aschner has indicated.

DR. JEFFCOAT: Let's take Question II-1 first.

Is that helpful to the FDA, Mr. Watson? III-1, excuse me.

MR. WATSON: Question III-1, okay. Assessing the strengths and weaknesses of clinical studies on dental -- I think I heard that -- I guess what I wanted to point out was I heard that there is still more work that needs to be done and that there were some flaws in the information that's there.

But I wanted to make sure I didn't -- I'm not confusing an answer that you gave here since the discussion has gone on a while, with maybe another question. I thought maybe you had also said go back and look at some newer studies, for FDA to do that. Is that -- am I hearing that correctly?

DR. JEFFCOAT: Yes, we were saying go back and look at some newer studies. Most of these studies were appropriate to ask the question, but like all clinical studies, they're not perfect and you do not necessarily get all your answers in susceptible subpopulations, which is why you would want to go back and look at more current patients.

MR. WATSON: Okay.

DR. JEFFCOAT: And then you're -- okay.

MR. WATSON: All right.

DR. JEFFCOAT: Is that --

MR. WATSON: But I think Peter has something to say.

DR. GOERING: Well, I think both of these questions address an

issue that we've had at FDA with these kinds -- with some of the clinical studies that we've reviewed and I'll just take Dr. Aschner's comment about the Echevarria studies. They did identify neurobehavioral effects at levels of urinary mercury that were very low.

However, there are other studies of dental personnel with much higher urinary mercury where they did not observe neurobehavioral effects. How do we deal with that kind of dataset?

I think, for the porphyrins, the same thing has happened. I think we've heard about porphyrin levels increasing in response to mercury vapor, but Jim Woods, Dr. Woods, at University of Washington, just published a study where they did not see any differences in porphyrin profiles between the composite cohort and the dental amalgam cohort in the Casa Pia trial.

So we have these -- you know, either we're dealing with very low levels of exposure where some studies will show effects, some studies will not show effects, and that's one of the issues that we have been dealing with and I think, when we were generating these questions, that was kind of some of the help that we are looking for.

DR. JEFFCOAT: Yes, Judith.

DR. ZELIKOFF: That's not very unusual for metals. You get hormesis. So if you're looking for something linear or something standard, it's very common to have effects at low levels of metals and have different effects in the medium and sometimes no effects at high levels. So I don't

think that's as surprising and I wouldn't negate the findings just because something wasn't seen at a higher dose.

DR. JEFFCOAT: Great. Dr. Ismail.

DR. ISMAIL: Amid Ismail. That's exactly the reason to do a systematic review and maybe a metal regression because when you have a small sample size, you run into these problems. So by combining the data and looking at all the factors and will be coded, the reviewer will look at all the factors published in the studies that could be included into metal regression that may explain some of these differences.

DR. JEFFCOAT: Yes, Dr. Bates.

DR. BATES: Also I'd suggest that probably to discriminate these studies, you probably need to get the raw data because if you rely on just published p-values and that sort of thing. Small studies have high p-values and you might think oh, there's nothing going on there but you get the raw data and you compare the actual raw data and different studies. You may find they're actually quite consistent.

DR. JEFFCOAT: Okay.

DR. STANFORD: Can I --

DR. JEFFCOAT: Who said can I?

DR. STANFORD: Clark Stanford.

DR. JEFFCOAT: Clark.

DR. STANFORD: I would offer and I would defer to the

biostatistician that this is a Bayesian support.

DR. JEFFCOAT: Um-hum.

DR. STANFORD: This is not a p-value approach because you're really looking at likelihood indices here and that's the kind of approach that needs to be taken.

DR. JANOSKY: You know -- and actually -- this is Janine Janosky.

Actually, some of the Bayesian approaches have been developed through CDRH, so --

DR. JEFFCOAT: Okay. Dr. Kotagal. Oh. Who was first?

Dr. Griffin.

DR. GRIFFIN: Yeah, I'll have to -- and say welcome to the world of toxicity value development. Yeah, you really do have to go back to the original studies. You have to look at the study protocol, dosing regimens, the whole design, everything, to determine, in your own mind, what the strengths and the weaknesses of the study is. And people will always second guess you, no matter what you do.

So as was mentioned earlier, there's a lot of new data out there. I think there's some very compelling evidence to suggest no effect levels for these effects listed here and it's just going to be a critical evaluation of the studies to determine what you consistently see as a no-effect or a low-effect level.

DR. JEFFCOAT: Right. Now, Dr. Kotagal.

DR. KOTAGAL: Thank you. Suresh Kotagal.

I just wanted to indicate that some work have already been done. There is a meta-analysis titled *Does Inorganic Mercury Play a Role in Alzheimer's Disease*, a systematic review. Came out in the *Journal of Alzheimer's Disease*, 2010, Volume 22, page 357. It is by the -- Mutter, M-u-t-t-e-r, from Germany, and they systematically reviewed -- two reviews. Reviewed 1,041 references, 106 studies filled in inclusion criteria, and most studies were case controlled and compared cohorts. So in 32 studies of -- testing in memory in individuals exposed to inorganic mercury, found significant memory deficits. So some work is there and I have this reference.

DR. JEFFCOAT: Okay. Can we go on to -- oh, okay.

Dr. Tinanoff.

DR. TINANOFF: One last thing --

DR. JEFFCOAT: Get a break when we get to go on.

DR. TINANOFF: I just want to just reiterate this. This is something that -- we've talked about things that are very hard and we've talked about measurement of these -- risk a lot and we can do something -- the FDA can do something very simple, is look at benefits or if there are benefits, what percent benefit is there of amalgam versus composite. This is a key issue for the patients and for the dentists. And if, say, for instance there is no benefit, then it's very important.

DR. JEFFCOAT: Um-hum. Thank you, Dr. Tinanoff, for that

wisdom.

Have we answered III subset 1 to your -- helpfulness, at least?

MR. WATSON: Yes.

DR. JEFFCOAT: Okay. Subset 2: Do the clinical studies support a relationship between exposure to mercury vapor from dental amalgam and adverse health effects, and I won't read them all off, and are there other adverse health effects?

And we felt that certainly, in the studies some tests were not sensitive enough to pick it up; in some cases, inappropriate endpoints were used and we really can't 100% tell what's going on in this appropriate subset analysis, so as -- go back and read this more current literature, it may be there because the n will be big enough.

Are you going to correct me or are you going to -- no, no. You can correct me. I'm saying a consensus statement. You can correct me. Does this -- yes, sir.

MR. WATSON: So this is Anthony Watson. What I'm hearing is go back and look at the most recent information. I mean, this is basically both 1 and 2, it sounds like.

DR. JEFFCOAT: Right. That's why I was --

MR. WATSON: Right. And I just want to point out that we'll go back and we'll do that, but we could end up in the same situation we're in now. I just want to put that very clearly, we could end up in the same

situation where we are now where the data are inconclusive and we will actually do exactly what you just mentioned a minute ago is then we'll have to make some judgment calls about benefit and risk, those types of things.

DR. JEFFCOAT: Um-hum. Absolutely.

MR. WATSON: Thank you.

DR. JEFFCOAT: Yes. Now Judith. But we're not on a question.

DR. ZELIKOFF: I'm clearly saying, for Question 2, Section III, that I don't think some of the important endpoints were evaluated in those clinical studies.

DR. JEFFCOAT: I said that.

DR. ZELIKOFF: Okay.

DR. JEFFCOAT: They have that.

DR. ZELIKOFF: I also just wanted to add that in the autoimmunity and allergy, I know there is a label on the FDA indicating, contraindicating if you're allergic. It's associated with certain types of polymorphisms associated with the HLA antigen and all and a number of people, when they come, are not going to know that they're either allergic, hypersensitive, to nickel or to mercury, and there -- it's difficult to put it on there because the majority of people are really not going to know unless they get this rash on their earlobe or unless they have, you know, shellfish in a humungous amount, and so the effects that I talked about in terms of autoimmunity, particularly, are associated with those polymorphisms in

susceptible subpopulations, so again, that has to be a real consideration.

DR. JEFFCOAT: Thank you.

All right, we will now have a short break for 15 minutes. I again caution the Panel members, please do not discuss any meeting topic during the break amongst yourselves or with members of the audience. We'll resume at 3:40.

(Off the record.)

(On the record.)

DR. JEFFCOAT: Okay, at this point we are going to continue with the FDA Panel questions and Panel deliberations. It's now 3:40 and I would like to resume this Panel meeting. We will continue with our discussion on the FDA questions.

Panel members, in order to help the transcriber, please say your name, and that includes me. Identify yourself each and every time you speak.

And we are on to Question III, Human Clinical Studies, 3. And does FDA want to present that?

MR. ADJODHA: Yes, thank you. This is Michael Adjodha. I apologize, it should be 3. It's not labeled on this slide.

So we have this statement and I want to put it into context. So when FDA issued the final rule in 2009, it issued a special control and a special control is the guidance document and it includes labeling

recommendations. And this statement here is something that has to be placed on the label of every amalgam package that is to be marketed. So the manufacturers place this statement on there with the other labeling and the label goes to the dentist, who will read this.

So that's the context of what I'm about to read. I'm not going to read the whole label, but FDA is actually is asking about the highlighted language and to discuss whether FDA appropriately represented the strengths and weaknesses of the available clinical data. And the highlighted language is as follows:

Clinical studies have not established a causal link between dental amalgam and adverse health effects in adults and children 6 and older. In addition, two clinical trials in children age 6 and older did not find neurological or renal injury associated with amalgam use.

The developing neurological systems in fetuses and young children may be more sensitive to the neurotoxic effects of mercury vapor. Very limited to no clinical information is available regarding long-term health outcomes in pregnant women and their developing fetuses, and children under 6, including infants who are breastfed.

So again, focusing on this language, discuss whether FDA appropriately represented the strengths and weaknesses of the available clinical data.

DR. JEFFCOAT: Now these clinical data fall into two categories,

if I may, the epidemiologic data that we have in the literature and of course the clinical studies and clinical trials data. Okay. So when you're discussing them, I think it would be helpful, certainly to me -- and I'll call on you, Norm -- if you just tell me what type you're referring to. And thank you.

Dr. Tinanoff.

DR. TINANOFF: This is Dr. Norman Tinanoff. I just think that it's important for us to add another sentence after the words children age 6 and older, and that additional sentence is: There may be certain populations that are more sensitive to the mercury in dental amalgam. Or some wording like that.

DR. JEFFCOAT: Yes, Ms. Rue.

MS. RUE: This is Karen Rue. I think the issue, to me, is about safety for the consumer, and I really said this earlier and I really think it's important, and it's about their health not just for today but 40-plus years from now, as well as the unborn. And I think it's imperative that we not so much say what we do know; it's about all that we don't know, that we haven't be able to determine, and what has been alluded to is just as important. Thank you.

DR. JEFFCOAT: Was that -- yeah, okay. Okay, other statements? Yes.

DR. JANOSKY: Janine Janosky. I'd like to return to the issue that I had raised previously with a distinction and a very important distinction

between causal links and cause and effect and relationships. And if I read what is in a box on our document and what is highlighted up there, these statements address cause and effect or causal links and there are no statements regarding relationships. And the FDA did ask us to address Number 2 under III, regarding whether we felt that there were relationships between the use of amalgams and adverse health effects.

The Chair of the Panel just mentioned in the introduction today that both of these are contained within there, if I'm paraphrasing correctly, and I don't see the issue of relationships in the message of the packaging that is going to the dental --

DR. JEFFCOAT: Oh, I didn't say that they were here. They were both in 1 and 2 that we addressed.

DR. JANOSKY: Yes.

DR. JEFFCOAT: Yeah.

DR. JANOSKY: Thank you.

DR. JEFFCOAT: Just to clarify what I thought I said.

DR. JANOSKY: Yes. So my question is related to the difference, it is a very important difference, and either returning to the 2009 explanation and/or whether we should discuss today whether the issue of relationships, and perhaps our understanding of whether those are found or not found between the use of amalgams and adverse health effects, should be placed within this box.

DR. JEFFCOAT: Yes.

MS. RUE: Karen Rue. I'd also like to say that whatever is given to the dentist needs to be given to the consumer in verbiage that is understood by them prior to procedure.

DR. JEFFCOAT: Yeah, this is packaging information and obviously this is a professional product. So what would go to the consumer would have to be totally different.

MS. RUE: Right, but it'd have to be the same information but in a different verbiage.

DR. JEFFCOAT: Right.

MS. RUE: The FDA person said it was going to the dentist. There was no comment that it was going to the consumer and it needs to go also to the consumer.

DR. JEFFCOAT: Well, you can speak for yourself. I believe you were just saying that this particular information goes to the dentist.

DR. JANOSKY: Right, that's what I understood and sometimes I'm not even sure that the dentists read. I think somebody in the office opens the packages and does whatever needs to be done, the assistant or the nurse, and then that's in the trash. So I'm not sure it always gets paid enough attention to. I don't know how to prevent that.

I think if something goes into your mouth -- you know, often if a doctor gives me a medication, he gives me the package to take home that

he's not using, rather than putting it in the trash, and I read the insert and the box and the black box.

DR. JEFFCOAT: Yes, Dr. Bui.

DR. BUI: Michael Bui. This is a question for the FDA. I need some clarification. I haven't had a chance to see the label. My question is, where is this language located in the label?

MR. ADJODHA: When an amalgam package is mailed out, it's an insert in the package.

DR. BUI: I understand that, but where exactly in the label is this language located?

MR. ADJODHA: I think, because it's such a lengthy statement, it's really just an insert and the pack is not -- I'm not sure if it's attached to the instructions for use or if it's a section of the instructions for use. I have not yet seen this language incorporated in the labeling currently on the market.

DR. BUI: Yeah, to me personally, I think this language is very important and how you place it strategically in the label can make a significant difference. I can use several precedents of how labeling is done in the pharmaceutical industry.

Given this language is so important and the concern about mercury, you know, is something the FDA might consider where it's placed in the label, would the FDA consider having a black-box warning similar to what

is used in the pharmaceutical labeling right now? Should the language be in the warning/precaution sections of the label?

I don't know how it's labeled right now, but I think that's something that the FDA should consider seriously, how it's placed strategically in the label.

DR. JEFFCOAT: Yes. What? The statement in the box is what we're talking about. The question was -- turn your microphone on. That's why nobody can hear you.

DR. BURBACHER: We were just talking here. Is the statement in the inserts, the whole thing, or just the box?

DR. JEFFCOAT: We're supposed to be discussing the box, according to the FDA.

DR. BURBACHER: Yeah, I just wanted to ask whether the whole thing is in --

MR. ADJODHA: Yes.

DR. BURBACHER: It's the whole thing?

MR. ADJODHA: Yes, the whole thing.

DR. BURBACHER: Thank you.

DR. JEFFCOAT: Yes, Dr. Bates.

DR. BATES: I'd just like to support Dr. Tinanoff's suggestion, which got quickly passed over, but I just wanted to come back to it, about the sentence, "may be susceptible to some groups". I forget exactly how you

phrased it. But I'd like to suggest that we just extend that a little by saying that at present we have no way of identifying susceptible subjects.

DR. JEFFCOAT: Yes.

DR. BURBACHER: The second part here indicates that there's no clinical information available regarding long-term health outcomes and I'd like to extend that to children, because we were just talking about that long-term health outcomes have not been studied in children, so it's not just limited to fetuses and children under 6.

DR. JEFFCOAT: Dr. Anusavice.

DR. ANUSAVICE: Ken Anusavice. The only thing I'm a little bit uncomfortable about is singling out amalgam only in this regard, because I think the same thing applies to composites, the alternative, especially bonding resins and so forth. There are references I can give you that show chromosomal damage associated with some of these resins.

So we're singling out one material, but then this was the topic of this conference and this meeting and so I just wanted to go on the record in saying let's not ignore all materials that may have the same question raised about them. Thank you.

DR. JEFFCOAT: Yes.

DR. KOTAGAL: Suresh Kotagal. With regard to the sentence two, where it states: In addition, two clinical trials in children age 6 and older did not find neurological injury, I would suggest inserting age 6 and older with

follow-up of up to 7 years, because there was no long follow-up.

And also I wondered if it would make sense to add another sentence, in keeping with what colleagues in the Panel have said: It is not known whether the lack of toxicity in children will endure with the longer follow-up.

DR. JEFFCOAT: I think the wording -- I'll be with you in a moment. The wording that I'm used to seeing in packaging inserts usually says things like longer follow-up has not been reported. Okay. Studies in pregnant women have not been performed. Because you can't make a judgment call on a study that hasn't been done. And again, this isn't the consumer version where you're going to walk them through what that may mean to them.

You have a point you want to make?

MS. DE LUCA: Jo-Ellen De Luca. I would like to suggest putting, before the clinical studies in the first paragraph, this concerns mercury, and start off with the subject and then let the dentists draw their own conclusions from the remainder. But I think that would make them more likely to share with the patient.

DR. JEFFCOAT: I need a clarification from the FDA. The device you're describing is dental amalgam. It's not a bottle of mercury, right? So I mean -- yeah. So yeah, I know that, but --

MR. ADJODHA: Right, right, it's a finished form of dental

amalgam.

DR. JEFFCOAT: Yeah. Okay. Yeah, Dr. White.

DR. WHITE: Joel White. I think all of us are jumping on to things that aren't said in the document, which is perfectly fine because these are things that you can consider that would have effect today. And I have a lengthy list. I just want to make sure I get them all out there.

What's not said is it's not safe for use by everyone. We'd all agree with that, it's not safe for use by everyone. Regarding pregnant and nursing women, dentists should consider not placing them. Because of the unknown risks, dentists should consider not placing in pregnant and nursing women. Dentists should consider not placing in patients with neurologic or kidney impairment or function. Avoid placing in patients who have allergic or hypersensitivity to mercury.

The labeling should also include some language regarding should consider reducing mercury exposure levels to the environment, to the patient and to personnel, as well as using accepted protocols for safe handling, safe use, safe disposal and safe removal from patients.

And then the last part of what was clear here is that the informed consent piece should be included somewhere in there as well.

DR. JEFFCOAT: Okay.

DR. BURBACHER: There was one group missing and that's the under 6 group that you didn't mention.

DR. JEFFCOAT: Dr. Fleming.

DR. FLEMING: Thank you. My understanding is this is under information for use, is that correct, do you think, in the -- I don't think it's under instructions for use. It's under information for use.

DR. JEFFCOAT: No, this is information. Yeah, that's right, yeah.

DR. FLEMING: On the label. Yeah, okay. If we make recommendations to change this label, there are certain aspects of it that might need to go under contraindications as opposed to general information. And there is a profound difference between the two, as I understand it, in terms of the obligation of the practitioner not to use it in a particular subgroup that you identify in the contraindications.

So if we say it should not be used in a pregnant woman, then that seems to be more a contraindication as opposed to information for use. I think you could do it either way.

I have some other concerns about this particular approach. I think this entire section needs to be rewritten to reflect what we're talking about here. You know, I am concerned about affirmations of safety in the absence of science to support that safety in these populations. That's my biggest concern as I read this. How can we justify safety, reasonable assurance, in the face of no clinical evidence?

DR. JEFFCOAT: Dr. Ismail.

DR. ISMAIL: It follows what Dr. Fleming said.

DR. JEFFCOAT: Yeah. Oh, okay, wait a minute, we need to get Mr. Watson.

DR. ISMAIL: Sorry, sorry.

MR. WATSON: I just wanted to follow up on what Dr. Fleming said. This is Anthony Watson. The contraindication, just to be clear, does have actually a regulatory requirement on our part, which is that it has to have data to support a contraindication. We can't presume an effect and state that in the label. We have to say we have data to show you do not use it in this circumstance.

So I just wanted to be clear that it really isn't a choice where we put it. If there are data to support it, we can use it as a contraindication. But in the absence of that data, it cannot be a contraindication. Sure, absolutely. Okay, I just wanted to clarify that.

DR. WHITE: So Joel White again. I just want to be sure that I -- I said should consider. I did not say contraindication. I can't go that far, but I can go as far as to say that, you know, people -- dentists and their patients should consider.

DR. JEFFCOAT: Okay.

DR. ISMAIL: That's me.

DR. JEFFCOAT: Who else is -- now we're on Dr. Ismail and then we're on Dr. Aschner.

DR. ISMAIL: Amid Ismail. I go back to what Norm said,

Dr. Tinanoff said. I think we need to recognize that there are some case studies documenting some detrimental effects of amalgam restorations in some patients who may be sensitive to mercury. I think that has to be recognized in the document because these cases are on the website, they're on YouTube, they're everywhere and people see them. However, large clinical studies have found no consistent association between amalgam and all the conditions. And that's also documented in the studies that we have and the studies that are published but have not been included in the docket of the studies.

I do suggest that we address another statement in this section, which is the lack of data on children less than 6 years of age, and make a clear statement that there are no data for that. Though we have the adjustment factor, the uncertainty factor adjustment and so on, we don't have the data for that and we need to be clear about that.

DR. JEFFCOAT: That is stated here. That's here.

DR. ISMAIL: It's stated in a very vague way.

DR. JEFFCOAT: You'd like it to be its own sentence?

DR. ISMAIL: It's own sentence.

DR. JEFFCOAT: Okay.

DR. ISMAIL: And stronger.

DR. JEFFCOAT: Very limited, no?

DR. ASCHNER: It's more of a comment and I don't know how

one deals with it, but I'm disturbed by statements such as in the presence of data, the FDA can use a contraindication; but in the absence of data, we can assume that something is safe. It just doesn't jive for me.

DR. JEFFCOAT: Through the Chair, I'm going to take that question to FDA.

MR. WATSON: Okay, if I said that, I apologize. I was saying that you --

DR. ASCHNER: You didn't say the second part. You said the first part.

MR. WATSON: Okay, okay, I just wanted to be clear.

DR. ASCHNER: In the presence of data, we can say that something is contraindicated. But in the absence of data, I'm saying we can state that something is safe.

MR. WATSON: Oh, okay.

DR. ASCHNER: I mean, it seems to me that's the extrapolation.

MR. WATSON: All right, I just wanted -- I didn't say that, so I just wanted to make sure that wasn't me saying that on the record. Okay.

DR. JEFFCOAT: Dr. White.

DR. WHITE: Joel White again. I think that if we're willing to hear about these adverse events and see these individuals come and tell their stories and we accept that as some credible case study, we also should be open-minded to the fact that there have been a lot of restorations placed,

that we've seen plenty of testimony here and plenty of case studies and lots of literature showing that restorations have been serviceable and last a very long time in this category.

So to say that there isn't safety data doesn't -- as a dentist, as a scientist, there's plenty of safety data. There's tons of safety data. I don't think we need to go back and prove safety of dental amalgams. There is a lot of safety of dental amalgams that are out there and there's a lot of safety information just in this room. I think we're on a roll and I -- well, you can look at the longevity of restorations and the published data --

DR. JEFFCOAT: Wait a minute. Excuse me.

DR. WHITE: Okay, thank you.

DR. JEFFCOAT: You need to be recognized by the Chair and if you have something you want to say, you need to be recognized and come to the podium.

DR. WHITE: Thank you.

DR. JEFFCOAT: I want Dr. White to be accorded the courtesy to finish his statement.

DR. WHITE: And I'll finish in 20 seconds. In the end, I don't think it serves us well to fight that battle, that it serves us well to look at improving upon the labeling. And we're on a roll here describing and helping FDA and giving them guidance, so I'd love to see us get back to that. But I just wanted to make sure that there is -- I am convinced as a clinician, as a

scientist, that I don't need any more information that amalgams are safe.

DR. JEFFCOAT: Since everybody spoke as a group, will you designate one of you to speak to this topic? Okay, identify yourself.

MR. LOVE: Jim Love.

DR. JEFFCOAT: And you have 30 seconds.

MR. LOVE: Thank you. We're skipping one legal step. I've listened all afternoon to what this very prestigious Panel doesn't know and there's a lot of data that we don't know about and a lot of you expressed concerns about an absence of safety data, recent comments notwithstanding. The solution is while we're missing that data, the product goes in Class III. Thank you.

DR. JEFFCOAT: Excuse me. I have asked you repeatedly not to give applause, not to interrupt, and I'm going to ask it just one more time.

Okay, other comments on what FDA -- we're here to answer the questions FDA has asked us, which do not have to do with a reclassification. Judith, and then I'll get him over here.

Excuse me, I did not recognize you. No, I have recognized someone else now.

DR. ZELIKOFF: Judy Zelikoff. I just want to -- I like Dr. White's additions that he would make to the label. I just want to add one point for consideration. Rather than a mercury allergy, I would like to submit that it say metal allergy. Since someone comes with a nickel allergy, let's say, given

the mechanism of action, there's a possibility that that person might react also to the mercury.

And I would like to echo -- I'm not sure who -- one of the Panel members mentioned it, about -- well, first, before I say that, I'd like to just get some clarification just for my own -- it was probably said, but maybe I didn't hear it. The yellow highlighted area, that is on the label currently?

DR. JEFFCOAT: Yes.

DR. ZELIKOFF: Yes. And the rest of the small print that is in the packet, it's all on the label? This is all on the --

DR. JEFFCOAT: It's all on the package insert.

MR. ADJODHA: I'm sorry, this is one statement.

DR. ZELIKOFF: Okay. May I ask you why we're focusing on that one section as opposed to some of the other sections? And one Panel member mentioned that he'd like to see a review or at least he had some comments on the other portion and I know I have a comment on one of the portions as well, that is not highlighted.

MR. ADJODHA: Well, you're free to give comments on the other portions. We just wanted to focus your attention on the clinical section of this statement.

DR. ZELIKOFF: Well, I didn't want to go against the Chair or the Panel, because we're focused on --

DR. JEFFCOAT: Yeah, let's finish what FDA has asked us --

DR. ZELIKOFF: Okay.

DR. JEFFCOAT: -- to do. And then if we still have a quorum, I will be more than happy to -- I personally would be more than happy to stay, if FDA is willing, so everybody can make their comments. And I know there's a comment over here. I think there was another comment before you, wasn't there? Dr. Bates, yeah. That's outside the yellow. We're going to take those later, if that's okay with the group, because we really need to finish what FDA has charged us with.

DR. KOTAGAL: My comment is outside of the yellow --

DR. DOURSON: Okay.

DR. JEFFCOAT: Okay.

DR. DOURSON: My comment will be very short. I support what Drs. White and Tinanoff are suggesting as far as additions. I had some other wordsmithing. They're not near as good as what they've suggested. I'll offer it to the Chair and then she can decide whether to pass it on to FDA.

DR. JEFFCOAT: But the group has to hear it because it's a consensus.

DR. DOURSON: Okay. So the other possibility is you can lead with the second paragraph first.

DR. JEFFCOAT: Oh, okay.

DR. DOURSON: Okay, you can lead with that paragraph first. You can then take your first paragraph as the second and just put the word

however in front of it. And then the additions, I think, Drs. White and Tinanoff have suggested are actually superior to that minor addition or thing. Thank you.

DR. JEFFCOAT: Yes, Dr. Aschner.

DR. ASCHNER: I think the FDA should be consistent. We heard you talking about amalgam, but you specifically addressed, in some cases, mercury vapor, mercury. So you can talk about the final product and then come back and talk about mercury. And you have a few sentences that talk specifically about mercury vapor and mercury.

DR. JEFFCOAT: The FDA should answer that, but I'd like to answer it as a practitioner because I need these sentences.

MR. WATSON: This is Anthony Watson. I would just point out that this gets to, I think, what some of the other folks have talked about, bringing out the components, talking about what we see happening and that mercury is part of the product. So I think that's why mercury is discussed in the label.

DR. JEFFCOAT: Yeah, I'm periodontist. I don't place amalgams. However, I need to know the products I buy. You don't have one agency approving them and another agency saying they're over the levels. And that's really what this is saying. That's what this is telling me as a dentist. It may be telling you something else, and obviously it is.

DR. ASCHNER: I'm sorry, but it says in the last paragraph -- in

the second paragraph, the last sentence says: Based on these findings, blah, blah, blah, amalgam do not put individuals age 6 and older at risk for mercury associated adverse health effects.

Okay, within the box it states, the first sentence: Clinical studies have not established a causal link between dental amalgam and adverse health effects in adults. To me these are two different things.

DR. JEFFCOAT: Okay, I'm trying to find where you are, which is my problem, because I think I read the wrong paragraph.

DR. ASCHNER: The fourth paragraph. I'm sorry.

DR. JEFFCOAT: The fourth paragraph. Okay, I read the wrong place.

DR. ASCHNER: The last sentence in the fourth paragraph says: Based on these findings, FDA has concluded that exposures to mercury vapor from dental amalgam do not put individuals age 6 and older at risk for mercury associated adverse health effects.

The first sentence in the box in the first paragraph says: Clinical studies have not established a causal link between dental amalgam and adverse health effects.

DR. JEFFCOAT: Okay, what goes outside the box we're going to take up after we finish the box, because they asked to do the box, okay? We just have to do it in some order, otherwise we'll kill each other here.

Okay, yes.

DR. STANFORD: Clark Stanford. Within the box --

DR. JEFFCOAT: Yes.

DR. STANFORD: -- I find it interesting, in a label, you are actually referring to two clinical trials, which have already been brought up this afternoon to have weaknesses. And yet the way this sentence is worded, it's very definitive. And I just wonder if, in terms of -- I would ask the FDA to perhaps consider reconsidering how that's written, because they say "did not find any neurological", and there's already been some assessment that the measurements used had some limitations, and renal injury, which perhaps has some limitations. So I'd ask that you modify that sentence if you want to leave such a sentence in the label, which is a little unusual that you refer directly without referencing the studies.

DR. JEFFCOAT: I believe, just so that I can get what I've got on the piece of paper here and I can -- it's a piece of paper and it can be changed. "In addition, the two clinical trials" -- this is what's on here from the FDA -- "in children age 6 and older with follow-up up to 7 years" -- that's what we added -- "did not find neurological or renal injury associated with amalgam use. It is not known what occurs after that time." That's what we added. That's what we added. Yeah.

DR. KOTAGAL: Suresh Kotagal. I would move that we strike -- that sentence one be struck and the second sentence, the in addition be taken out and just state the two clinical trials in children. I think the first

sentence is perhaps redundant.

DR. WHITE: A compromise? Sorry, Joel White. A compromise?

DR. JEFFCOAT: Any compromise? Yes, sir.

DR. WHITE: You might want to put something in about these tests did not test for all adverse health effects.

DR. JEFFCOAT: Wouldn't you need to say that in absolutely every document and sentence the FDA possibly put out? Just to ask the Panel that. Yeah.

DR. BURBACHER: I think probably all of us have tried to write something in a --

DR. JEFFCOAT: Yeah.

DR. BURBACHER: -- group this large and it never works.

DR. JEFFCOAT: It never works, that's right.

DR. BURBACHER: Yeah. So I think that they're asking us whether -- to discuss whether the FDA appropriately represented the strengths and weaknesses of the available clinical data. I think we can say no, we don't think they have. And we can maybe give them some areas where maybe the strengths are overstated or understated and where the weaknesses are overstated or understated. But I don't think it's worth our while to try to wordsmith everything for them.

DR. JEFFCOAT: Well, they asked us to wordsmith just this box. And basically I think all we need to do is tell them what we're not --

DR. WHITE: Did they ask us to rewrite it?

DR. JEFFCOAT: No, they asked us to tell them what else we want in it and what we may want out of it. Okay?

DR. WHITE: The strengths and weaknesses.

DR. JEFFCOAT: And I know there is someone out here from the public who wants to talk, but not right now. Okay, we have to -- but I'm just letting you know I haven't forgotten. Yes, ma'am.

MS. RUE: Karen Rue. There was discussion earlier about consideration for risk assessment and I didn't know if that was one of the things that Dr. White felt maybe should be added to suggestions for consideration, was a risk assessment. It was brought up earlier.

DR. JEFFCOAT: Well, that was in one of the previous questions and that was in the answer to the previous question.

MS. RUE: I know, but when he was talking about the laundry list of things that the professionals and consumers needed to consider, I just didn't know if it was something that you wanted added or not, a risk assessment of the patients.

DR. JEFFCOAT: How does the group feel?

DR. DOURSON: Mike Dourson here. I don't think you need to add that in the box.

DR. JEFFCOAT: That's true.

DR. DOURSON: I mean, there's other text later on that we can

suggest changes to that'll get to it. But if this is for your consumers, I think the additions that I've heard by Drs. White, Tinanoff and others -- yes, Doctor, I'm sorry. The suggestions you're making seem really reasonable to me and you don't need to add that risk part here.

DR. JEFFCOAT: Okay, do we have -- yes, Mr. Watson.

MR. WATSON: I'm loath to interject on a good conversation, but I wanted to just clarify. The exact wording is going to be difficult because I think people will go back and forth and kind of cut each other's words apart.

DR. JEFFCOAT: We know that.

MR. WATSON: And I've got to tell you, I know from my own writing, my words never make it through the first or third time. So I would just suggest, if you could, help us with what types of areas we should focus on strengthening the labeling.

So I would agree with your comment, unless you can come up with a really pithy statement that would get through the first time and everybody would agree with, which is rare.

DR. JEFFCOAT: It's not going to happen.

MR. WATSON: Yes, thank you.

DR. BUI: I'm here.

DR. JEFFCOAT: Yes, Dr. Bui.

DR. BUI: Michael Bui. I just want to share from an industry perspective, when it comes to labeling. You know, for labeling, just a lot of

negotiation between the sponsors and the FDA, this can go back and forth a lot of times.

I just want to make a comment. You know, for the labeling language it'll be concise. It has to be scientifically accurate. But you always have to consider the legal liability as well. And from an industry perspective of a company, we always think about legal liability when we word the language. So that's something I think that the Panel needs to take into consideration.

DR. JEFFCOAT: Okay, Dr. Ismail. And then you may speak.

DR. ISMAIL: Amid Ismail. I don't agree that the statement is incorrect. It may be incomplete. And the incompleteness in it is that there are other studies that need to be included and if we do the due diligence and go and do the whole literature -- there's been two or three additional studies included here -- it's not just children.

There are studies on adults as well that we need to include here to make it a complete statement that the consistency of the lack of causal relationship is there. There are case studies. That's fine, we can mention them, but in another section of the document. But there are large studies that show that there is a lack of causal relationship between the two.

DR. JEFFCOAT: I mean, if this were a drug, you'd be benching the two well-controlled, double-blind clinical trials, but this is not a drug.

Okay, would you like to speak for 30 seconds? And please

identify yourself so we get your name. And thank you for being patient, I appreciate that.

MS. MOORE-HINES: Thank you. Sarah Moore-Hines. I just wanted to mention that we've had over 50 consumers and other folks who have testified in the last 2 days about personal harm from amalgam. To my knowledge, all or most of it has been documented. So I would really ask the Panel to keep that in mind. If you're looking for some evidence, you've got live evidence here in the last 2 days.

The other thing is, my understanding is that there's no scientific evidence of safety for children under age 6, so unborn children or fetuses per se.

And I'd like to remind the Panel of the reference in my testimony, from the second page. A large scientific study by the U.S. Centers for Disease Control and the National Center for Health Statistics/NHANES III, in which thousands of people's health was monitored, found significant correlations between dental amalgams and several chronic health conditions, including MS, epilepsy, mental disorders, migraines, disease of the nervous system, disorders of the thyroid gland, cancer, and infectious diseases. And that reference is in my testimony. Sarah Moore-Hines. I hope that's helpful for the Panel.

DR. JEFFCOAT: Thank you. And thank you for your patience.

Yeah, okay, if you have comments on outside the box, I think

we have one other thing that the FDA would like us to comment on, so let's do that and then we can get the outside-the-box stuff in, because that can be -- yeah.

DR. TINANOFF: I want to comment on outside --

DR. JEFFCOAT: Inside the box?

DR. TINANOFF: Outside of the box.

DR. JEFFCOAT: Outside of the box. So let's do their last question.

MR. ADJODHA: So the final question. Michael Adjodha, FDA.

The first two sets of questions focused on exposure to mercury from dental amalgam and the appropriate reference exposure level to assess the risk of such exposure which factor into the risk assessment for dental amalgam. The third set of questions focused on the human clinical studies. Based on your answers to these three sets of questions, discuss how FDA should weigh risk assessment and clinical studies in considering its regulatory approach to dental amalgam.

DR. JEFFCOAT: Comments from the Panel? That one wasn't numbered, so you are speechless. Yes.

DR. WHITE: Joel White. I think the consensus was to use the available clinical studies to redo the risk assessment.

DR. JEFFCOAT: They're asking about their regulatory approach now. Okay, you're quite right and I believe they've heard us there.

MR. ADJODHA: So just an FDA point of clarification. We aren't asking for a regulatory approach. We're asking: How do you weigh clinical information versus risk assessment information? What would you place more weight on?

DR. JEFFCOAT: Risk assessment. Which would you place more weight on, the risk assessment or -- the risk assessment comes out of the clinical studies. Yeah, please help us.

DR. GOERING: Well, I am not a risk assessor, but I think the question is -- or my perception is that an agency could come up with a regulation on a product with just the risk assessment, finding a critical study, applying uncertainty factors and come up with a regulation. FDA doesn't often do classical chemical risk assessment as we're doing, as we've discussed the last 2 days. We do use a lot of clinical studies in making judgments and in coming up with a policy or a regulation. So I think we're asking about the weight of either approach and, of course, yeah, we know that using new data would help us find critical studies for the risk assessment part.

DR. JEFFCOAT: Okay, thank you for that clarity. That's helpful to me, so I am liking to think it's helpful to other people.

Dr. Griffin. We're going to go down that --

DR. DOURSON: I'll defer to the lady.

DR. GRIFFIN: You have a very difficult situation here, and with the risk assessment you're using a modeling approach that contains a great

deal of assumptions and uncertainties and it may result in estimates from amalgam that exceed different regulatory agencies' reference levels. And this you have to weigh against the clinical studies that are out there, the amalgam studies showing no effects, the occupational exposure studies showing effects.

Like I said, it's going to be a tough decision. Realize that the modeling approach is fraught with a lot of uncertainty in the assumptions that are used. You may, as Dr. Farland suggested, look at a margin of exposure approach. That may be more realistic. Europe, Asia, Canada all use that. And that's the best I could suggest. It's not going to be easy.

DR. JEFFCOAT: We're going to go down here, then we'll go to this table.

DR. O'BRIEN: Yes, Bill O'Brien. I am very familiar with the PDR approach, in which they discuss a particular drug. I know this is not a drug and I want to compare the PDR approach. They discuss a particular drug. They talk about the composition, something about the chemistry of it, and then they go into a clinical approach and they will have little tables of some of the percentage of effect of controls versus someone taking the drug that are in the clinical studies.

And then there's usually a third approach, in which they indicate all the possible problems and symptoms which I think this group is talking about, the public group. They list all the possible symptoms and

hopefully you don't get those symptoms. But they do expose that publicly, as to all the possible symptoms that have been reported with the drug.

Is that a different type of classification that I'm talking about in terms of a drug versus a material? In other words, you're not listing -- you're not following that general approach that gives a lot of information sometimes, Gary mentioned, but they don't limit that.

DR. JEFFCOAT: You're talking about the adverse event chart that you always see with a drug? Yeah --

DR. O'BRIEN: Right. That's right.

DR. JEFFCOAT: -- with the placebo, presumably if there's a placebo.

DR. O'BRIEN: Clinical studies give a reference.

DR. JEFFCOAT: And just so that everybody sitting in from the public actually could talk about it.

DR. O'BRIEN: I often think they're covering themselves, actually, because they list everything possible. Headaches, you know, stomachaches, whatever. And they often think they're covering themselves because they've disclosed it.

DR. JEFFCOAT: You ask the patient. I don't know if you do clinicals, but you ask the patient and you're bound --

DR. O'BRIEN: Yes.

DR. JEFFCOAT: -- by regulation and the law to report them if

they're serious. But we don't need to go into clinical trials 101. Yes.

DR. KOTAGAL: Suresh Kotagal. I may be overstating the case, but I think that children are different from adults and I think children need to be -- infants and children need to be addressed separately than the adults because of their increased risk. And I think that there really is perhaps no place for mercury in children.

Now, with regard to adults, I would suggest that we commission sensitive studies using sensitive biomarkers and that will help us define whether they are -- whether amalgam is equivalent to the other resins.

DR. JEFFCOAT: May I ask you a question for clarification? You said there's no place for mercury in children.

DR. KOTAGAL: Yes.

DR. JEFFCOAT: Based on data, based on experience in treating patients, based on what you heard here from the public? And it can be all of the above. It's just so FDA has a sense of --

DR. KOTAGAL: Certainly. I'm not a dentist, so I don't have any experience dealing with mercury amalgam. But based upon the review of the data that was presented by esteemed colleagues, and doing my own researches, based upon hearing the testimonials of the people here, I believe that -- you know, I mean, the bottom line in medicine says do no harm. I mean, we have to start with that tenet, do no harm, and then take it from there. So I think that's where I'm coming from.

DR. JEFFCOAT: Dr. Anusavice. And Dr. Bates, do you want to -- okay, we'll let Dr. Anusavice go. Sorry.

DR. ANUSAVICE: Ken Anusavice. My comment's related to risk, risk assessment, and it's my recommendation to isolate out the professional risk from the patient-related risk because they're two different things. I don't think they should be extrapolated from one side to the other, except in cases where we have absolutely no other recourse.

So the histories of dentists and dental practices varies widely. There are many confounding factors. They're related to the stress associated with dentistry and dental practice, that you just have too many variables that are not related to the patient situation. Or at least we must be very careful when trying to extrapolate or interpolate between those two populations.

DR. JEFFCOAT: Dr. Bates.

DR. BATES: Thank you. In regard to the FDA question about weighing risk assessment and clinical studies, my perspective on this is very simply that you define all the clinical studies' information and then you use a risk assessment or a modeling approach to extrapolate from there. If necessary, it may be that your clinical data covers the range of exposure, such as amalgam, in areas where it doesn't use a risk assessment or a modeling approach to extrapolate down to those. So that's how I see it. I don't see them as being either/or in terms of weighing one against the other. I think they're quite complementary.

DR. JEFFCOAT: If anybody didn't hear that, the bottom line was they're complementary approaches.

Dr. Tinanoff, you're the one who treats children all the time. I mean, I love to treat children.

DR. TINANOFF: I would just like to get back to the idea of looking at the risks and looking at the benefits. And both of those things are part of the formula. So if you have two products that -- well, I think the consumer needs to know that. A very simple thing. The consumer needs to know the risks and benefits of both products and they should be given the choice to choose which product they want to use.

DR. DOURSON: Mike Dourson here. So I've agreed just about with what everybody has said around the room as we've gone this way, and just go to the question, I don't think you need to separate the assessment at all -- I mean, the clinical side from the other risk side. A risk assessor would integrate those right away and take all of that clinical data and try to make the best you can of it, because really that's preferred data.

I like this idea of separating them out. Dr. Anusavice has talked about sort of an occupational level and perhaps more a consumer level. I think that's ideal. I like this idea of cost benefit. It makes a lot of sense to me.

So again, you don't have to separate it, you know, from a risk perspective or a clinical perspective, because if the risk people are doing their

job, they're listening to their clinicians and their colleagues in that area.

DR. STANFORD: This is Clark Stanford. I would support -- I'm a little bit -- the weight of the evidence here is weight of the evidence of the options that the clinician has in terms of addressing a significant clinical issue. And so when you're dealing with weight of the evidence, it's not just a material, it is all the options and the issues at hand in the clinical sense. And I agree with Dr. Tinanoff and what he was saying.

DR. WHITE: We've got a lot of good information here. I like risk assessment and I think it should be incorporated. And yes, it needs to be balanced with the eye on what's the exposure and how many restorations. The things that we've already talked about incorporating in the risk assessment will give us valuable information. So clinical data and risk assessment will both help the Agency and they should be balanced towards determining risk and benefit.

DR. ZELIKOFF: I don't have much to say. I agree with --

DR. JEFFCOAT: We want everybody to have a chance to weigh in on this one because it's so important.

DR. ZELIKOFF: Okay, I agree with Dr. Stanford and what he said. I just think that weight of evidence should not just consider certain studies but all scientifically sound studies that will add to or detract from the weight of evidence.

DR. JEFFCOAT: And the operative word there was scientifically

sound. Okay, I got you. Dr. Aschner.

DR. ASCHNER: Yeah, I also agree with everything that was said this last round, all the way from the beginning. You know, I think the important issue again is risk/benefit and I would question whether a 10-percent benefit, with all the uncertainties that we don't have information about, is worthy of consideration. And I'll stop here.

DR. JEFFCOAT: Yeah, in a comparison study, though, you'd have the risks on the other side.

DR. ASCHNER: Well, it was mentioned before that 10-percent benefit might be a good reason to mercury -- to amalgam. I'm sorry. And my question would be, with all the uncertainties, is it worthwhile using amalgam that contains mercury for a 10-percent benefit? That's my question.

DR. JEFFCOAT: Dr. Fleming.

DR. FLEMING: Mike Fleming here. Well, I'm in agreement with Dr. Dourson that the risk assessment and the clinical trials merge when you begin to do these kinds of things. I think, to be quite frank with the Panel, I've been in clinical practice over 30 years and have not used amalgam in 25 and I find this product to be not necessary in the clinical practice of dentistry. I am confounded by the fact that safety is -- or the use of the product is allowed in a population where there aren't -- there isn't enough data to support safety. It absolutely confounds me.

But having said that, there's so much more that needs to be

done, but we could be researching this forever. And what I would not like to see is for this to be a repeat of 2006, where the status quo was maintained. I think something needs to change. I think the ideas on this label are fantastic and I think that those changes should be considered and considered quickly. Thank you.

DR. JEFFCOAT: Dr. Ismail.

DR. ISMAIL: There has been a difficult 2 days, because we have to balance a lot of issues, both personal, professional and scientific. And I really thank the FDA, though you have been criticized a lot for what you do. Knowing the history of what you have done before to the public, you should be thanked all the time. You've saved this country from major disasters before.

The issue of amalgam and mercury has been going on since amalgam and mercury started. The amalgam war was part of the -- there as an amalgam war in the United States at a certain history between different camps within the same country.

We have extensive data that's from case studies, but also from large studies, experience of thousands and hundreds of thousands, millions maybe or hundreds of thousands of dentists around the world, that, overall, in the large population amalgam is safe. In a small population of patients, that may not be the case and we need to recognize that and that's very important.

How do we do the risk assessment? We can't do it after the fact, but we have to find ways to recognize that there are some patients who cannot -- should not have amalgam.

I am not in favor of banning amalgam because I want to keep the option for the patient and their informed consent situation where they're fully informed of the risk and benefits and for the dentists to decide with the patient, not for the patient but with the patient to decide what's the best alternative for that case.

And children less than 6 years of age, I would restrict it significantly and have the -- be clear that the data do not -- while the efficacy may be there in terms of the clinical practice, but that issues about safety, and so on, have not been documented very well. So we need to balance all what we have heard over the 2 days and come up to a conclusion here.

DR. JEFFCOAT: Dr. Thompson.

DR. THOMPSON: I would agree overall with Amid. What I was struck by in some of the stuff we've been going through and hearing expert testimony was the lack of threshold and the fact that it looks like this may be a linear response, which I unfortunately have the tendency to equate with lead or cadmium. And so I have serious concerns about this and think that really we have to look at informed consent; definitely not in pregnant women and definitely not in those below 6 years of age.

MS. DE LUCA: Jo-Ellen De Luca.

DR. JEFFCOAT: Okay, you've been cleared. I just was thinking through what you just said. Sorry, sorry about the delay. Ms. De Luca.

MS. DE LUCA: I think we always have to have safety first, look at the patient first. For some populations, I don't think amalgam should ever be used. Other populations, I think it definitely is a choice. I think it appears that most of the people that use the greatest amount of amalgams are those that have the least amount to save, poor children that live with lead paint at home and perhaps go to stores that still have the patient, with the lead paint around the windows and they shop and they eat all the same thing. And that does concern me. That always concerned me. For the general population, most people are today more aware.

I think things that we could do, and it would boost the FDA a lot, are to put a few articles in places like *Reader's Digest*, things that are -- *Highlights for Children*, or things that are in the doctor's office that would explain more about there are risks when we do things, even getting a filling. Because children don't know amalgam from mercury, from anything else and you know, they think it's a thermometer. So those are things that I would suggest. And all in all, I think the Panel has done a marvelous job.

DR. JEFFCOAT: In due respect, I think most of the little tiny ones have never seen a mercury thermometer. I mean, you know, they're used to the one in their ear, usually. Ms. Rue.

MS. RUE: I think the cost benefit analysis is excellent. I mean,

we have the opportunity to do that. And I'm very thankful for the discussions of safety and the patient awareness and education because that's what I feel the focus needs to be.

DR. JEFFCOAT: Dr. Bui.

DR. BUI: Yeah, I just want to share. I think the FDA is approaching the Panel and asking us for regulatory advice. In the industry, at least for the pharmaceutical industry, the FDA usually impose REMS in some products. I don't know whether that's applicable to the medical device industries. Some of the REMS components include -- a good example, I think, if I remember correctly, for Accutane they required patient registries.

To me, from the last 2 days or so, you know, listening to all the speakers and the public, I'm very concerned about mercury and I think that's something that the FDA might consider, imposing something like a REMS that would require patient registries. That would provide significant data to study long-term outcomes.

Another thing that the FDA might consider usually on a REMS component is that they would require patient education or at least, you know, for healthcare professional education to educate health professionals about a product itself. And that's something that the FDA might want to consider.

For the last 2 days I've listened to the public. You know, I think the point the public is making is that the public's not getting enough

information to know what's in amalgams and I think that's something that the FDA needs to do a better job at communicating that risk to the public, not just to public -- but to health professionals, both to the medical profession and the dental profession as well.

DR. JEFFCOAT: Thank you. Oh, okay, I thought you -- okay, I'm sorry, I apologize for skipping you. Yes.

DR. DMYTRYK: John Dmytryk. I just want to kind of echo what Dr. Kotagal said. I think really important, when we assess risk, we really don't want to lose sight of maternal mothers. He mentioned infants and children as being -- we need to look at them separately. Obviously, that implies that we need to look at maternal mothers separately because that's where they would receive their mercury from.

And certainly, again, as Dr. Thompson indicated, the small subset of the population that really seems to be highly susceptible, we really need to focus on them and not treat them the same as the general population.

DR. JEFFCOAT: Okay. And yes.

DR. BURBACHER: So I've got two comments. One is a comment about children. I think if you look at the various children's advocacy groups, children's groups that are looking at environmental health, as well as the Administration's program on children's health, the issue here is to reduce exposure to children. And I think that if we don't know what's going on in the

long term with this exposure that starts very early in life, that we should err and be cautious.

So why put amalgams in children if we know they're going to live with that for the rest of their lives? And we don't know what that's going to do. So do we have to prove that before we stop doing it, is one question. I don't think we should.

The second issue that I'd like to talk about is the risk/benefits. And that's fine for people who have the choice and we've heard and there are data now that indicates that the use of amalgams is going down in the U.S. But who are the ones that are continuing to use it? It's minority groups, it's poor groups that have no choice. Okay. So it's nice for us to talk about risk/benefits and choice, but if you don't have a choice, that discussion is meaningless.

So I just want to make sure of that when we're talking about risk/benefits, just remember that doesn't actually -- you know, it's not something that's going to affect all people.

DR. JEFFCOAT: Well, even when there are choices, people make choices for different reasons that aren't always -- for example, when we're giving free dental care to people who cannot afford dental care, they often choose amalgam for that 10%. Okay, no, that's the absolute truth.

It's because they don't -- they've been told the risks. They've had it in writing, as we knew it at the time, which was only a year ago, so it's

not very different from today. But the 10% means you don't have to go to the dentist so fast. And if you're terrified of the dentist, you will make a different set of decisions.

And all I'm saying is people -- part of informed consent is you're allowed to make decisions for different reasons and the regulatory agency is there to see that, if it's real bad, it's not there. You don't have that choice because I can't buy it, as a dentist, to put it in. And as I said, I'm a periodontist, I don't use that.

DR. BURBACHER: I mean, just to respond just very shortly.

DR. JEFFCOAT: Yes. I know you don't believe that, from the look on your face.

DR. BURBACHER: I mean, there are -- no, I believe it because you wouldn't be tell me if it weren't true.

DR. JEFFCOAT: No, I wouldn't.

DR. BURBACHER: I believe you. My comment was that there are people who won't have a choice and --

DR. JEFFCOAT: Yes, I believe that is absolutely true.

DR. BURBACHER: -- those people tend to be the ones, as someone mentioned here, who have a lot of other environmental problems, have a lot of other societal problems. So it's the one that's are already, you know, having lots of problems with other sources that are going to be the ones left.

And then, you know, the second part was just, you know, when you talk about if it's safe, I mean, what are you going to call safe? I mean, if we don't know in the long term that these early exposures are safe, is it better to just go ahead and keep doing it or is it better to say, well, we'll err on the side of caution and not do it, since we have alternatives?

DR. THOMPSON: Could I address that one?

DR. JEFFCOAT: Who's saying that? Yes. Van, I should know your voice, I'm sorry --

DR. THOMPSON: Oh, sorry. Van Thompson.

DR. JEFFCOAT: -- after 2 days.

DR. THOMPSON: Going back to what you were talking about, choice and coming back and that sort of thing. I think that what's missing now is the fact that the databases that the insurance companies have over the last few years, and others, would point out that the longevity of composites is equivalent to, if not perhaps better, than amalgam on a comparative basis.

And the other part of is even the ADA came out in 1998, saying that the initial -- for initial lesions, resin-based composite, at least for moderate-sized lesions, resin-based composite was the material of choice because of conservation of tooth structure that you could achieve. And we basically know that the smaller the restoration in general, the longer it lasts. Okay. So all of this points to why composite is equivalent to, if not, you

know, moved along, compared to amalgam.

So from a benefit point of view, I don't see it for amalgam at all. And so it raises the question -- where we are with it. We have members of the Panel who don't use it. We certainly don't only teach it to make sure that people probably can pass the boards at New York University. We don't use it at all if at all possible.

DR. DOURSON: Mike Dourson here. A quick question for Dr. Fleming. Dr. Fleming, the thing that we haven't really talked about a lot is the toxicity of the composites, the risk from them. In your 25 years or 20 years of practice with composites, anecdotally, have you noticed any sort of risk in patients that have had the composites? What are your thoughts on that?

DR. FLEMING: I think over the 30 years that I've used the product, and then full time on it, and other alternative materials as well since then, there are two forms of composite that we use in dentistry, essentially. One is for filling materials and one is as a cement for our modern crowns, that go under our crowns.

So I must say I have not seen any reactions of the type that we're discussing here. That doesn't mean there never would be, particularly if they have a petroleum-based sensitivity of some kind. Some of these products are derived, or were, from petroleum.

But for the most part, the concern over BIS-GMA, I think, so far

the results are very encouraging. I understand that there is some research that's been done which indicates that the amounts are exceedingly small of BPA, which is an issue for dentistry. Some of the leachates are being analyzed as we speak.

DR. DOURSON: Okay, thank you.

DR. JEFFCOAT: But in big practice, you are going to have -- I don't mean you per se, but one is going to have some patients who have autoimmune diseases and some patients who have -- and that's of course why you end up needing to do risk/benefit analyses and trials or studies to know that, because on an individual basis, it's a disaster. But you can't ever even show -- you can show a relationship, but you can't ever get close to causation on an individual basis.

Yes, Dr. White.

DR. WHITE: Joel White. I just want to make it clear that methacrylate sensitivity does exist and there are people who do respond negatively to composites and they do have a myriad of symptoms. Many of them are very rare and severe. So I just want to make sure that -- not everything is risk free.

DR. JEFFCOAT: We do not have time for questions from the public. Yes, you can --

DR. KOTAGAL: Suresh Kotagal. Just one quick comment in response to what some of my esteemed colleagues had said. You know, I've

been a pediatrician for 34 years, a pediatric neurologist for 31 years. I don't see the difference physiologically between a 5-year-old and a 7-year-old. I think the artificial cutoff at 6 and below, I think that has more to do with the completion of some psychometric tests which are sort of designed for 6 and above, et cetera.

DR. JEFFCOAT: You need to be able to read, you think? Yeah.

DR. KOTAGAL: So I would submit and my plea would be that if there is a change, if a change is made, that it be made in infants, children and prepubescent children. So really all children below puberty are -- all infants and children below puberty are taken into consideration, because there really is not a whole of difference between a 7-year-old and a 5-year-old.

DR. JEFFCOAT: Does one of the dentists want to comment on really assessing whether someone is through puberty in a dental office?

DR. TINANOFF: I agree with that statement.

DR. JEFFCOAT: So you could live with that and you feel that you would know with a high degree of assurance?

DR. TINANOFF: I agree with -- I don't have data, but I --

DR. JEFFCOAT: No, no, no. I mean whether the patient is through puberty. That was my question. It was an easy question.

DR. TINANOFF: Well, maybe we could just say 12 and under, because --

DR. JEFFCOAT: Can you live with that?

DR. KOTAGAL: Sure.

DR. JEFFCOAT: Can the Committee live with that? Okay, let me ask the FDA -- okay, go right ahead and then I want to ask the FDA if we've answered their questions and then I'm going to ask the FDA if they would please stay because we've got time to address the questions -- the comments you all had outside of the box, okay, because I think there were lots of them and I did not hear you. Dr. Griffin.

DR. GRIFFIN: I just want to address the last comment, in that it seems to run counter to the clinical studies that were conducted in New England and Portugal, in which 8-year-olds and older -- actually 7 and older were tested for neurological effects. So that's one area we do have data in, although I would agree with you, in the younger children, we don't seem to have that data.

DR. JEFFCOAT: Yes.

DR. TINANOFF: But remember that data is very short term and again, it's whether or not, in the absence of having long-term data on early exposures, do you go ahead and do it or do you recognize that kids up to -- well, actually it's 20. Their brains are still growing. You know, their systems are still growing and basically indicate that, you know, they are a sensitive population that probably should be minimally exposed.

DR. JEFFCOAT: Judith and -- okay, let's keep this to -- so that we can get through what all of you wanted to get through, because you're

going to get --

DR. ZELIKOFF: Okay, I just want to --

DR. JEFFCOAT: That wasn't addressed only at you.

DR. ZELIKOFF: Oh, I know. I just wanted to make sure that, as Dr. Burbacher said about the brain, that the lungs are growing and changing over time and we're talking about inhalation as well. And so we have to take that into consideration.

And I just want a point of clarification. In weight of evidence we're looking at clinical studies. Why does, or why does not, the FDA consider animal studies?

DR. GOERING: We did consider animal studies. We discussed those in the White Paper and in the addendum to the White Paper. We discussed the inhalation mercury vapor studies done at NIEHS, where they exposed pregnant dams and followed neurobehavioral endpoints in the offspring. Those are some studies that come to mind.

DR. ZELIKOFF: I was primarily asking because all of the questions that we've had as Panel homework were addressing clinical studies, which gave me the impression that that's where the weight of evidence was coming from. And I would like to just -- I'm glad that the FDA has looked at animal studies and I think that's a very important biological plausibility that needs to be established.

And I'd also like to just make a plea for consideration that, as

we heard the first day from Dr. Aschner, that mercury was not mercury was not mercury. I'd like to say, however, that much can be learned from inorganic mercury or possibly that methylmercury, when it gets into the cell and has an action, may be an inorganic mercury. So I think that we should also, when appropriate, look at some of the outcomes from some other mercury species.

DR. JEFFCOAT: Okay, may I ask, Mr. Watson, we have essentially two questions here that we have not asked you. One has to do with the box and the other has to do with the weight of the evidence. Have we provided you with information that is useful to you? Well, maybe.

MR. WATSON: Yes, the weight of the evidence, it was a very wide range of discussion, I'll put it that way. I wanted to comment real quick, if I could.

DR. JEFFCOAT: Please.

MR. WATSON: The weight of evidence. One thing that's not really stated in this question is that we often make decisions, especially when we put products on the market, based on clinical information or some positive evidence on that device. Risk assessment is something that happens usually in the background, but it's not typically a threshold decision for us.

So we've heard throughout all of this discussion, you know, there were risk assessments that were challenged, there were clinical studies that were challenged, and this question really is about, okay, so when you're

trying to relay information to people, where do you put that balance? But what I'm hearing is could be both. All of that should be very well represented and we basically have to go back and do some of our own homework to come up with some of that risk assessment information ourselves.

So I think we did hear some information we could work on and out of all of that, some of the questions -- some of the answers went to actions we could take and of course we have to fit that into what our actual regulatory burdens are. So we'll have to go back and look at that.

The last comment I want to make is that there's no need to go back to that label again, because that box section is really important for us to work on and all that other language is basically based around information we've got in that little box. So we're going to go back and rearrange that box and based on the information you gave us, which is the really important stuff for us, then all of that other information could very well change.

And I do have one more comment. The concept of, I heard, you know, do no harm -- and everybody, I think, would love to live in that world. I think the reality is that there's risk with everything we put on the market, even a scalpel, which, by the way, is a Class I device, can do harm.

So we have to balance the risk here and make some decisions based on that. But the information that you've given us today is very invaluable and we'll go back and look at what we have. So thank you. That was a longwinded answer to your question, but I wanted to make sure we --

DR. JEFFCOAT: Well, thank you very much. Does anyone on the Panel have other comments to make, including the area outside the box? Yes, Dr. Bates.

DR. BATES: Just in regard to the area outside the box. I just want to note that it talks here about the ATSDR and the EPA's established levels of exposure. We are proposing here an FDA level.

DR. JEFFCOAT: Um-hum.

DR. BATES: So that would need to change, assuming there is some action taken.

And then the other thing is, it states in the second paragraph below the box, that reliable methods have shown that dental amalgam exposes adults to amounts of elemental mercury vapor below or approximately equivalent to the protective levels of exposure. I'm not sure, based on Dr. Richardson's data yesterday, that that is true. It seems like quite a few people could be exposed to levels above those.

DR. JEFFCOAT: I believe, if the FDA chooses to act on our suggestion, those numbers may -- Dr. Richardson's numbers may be recalculated.

DR. BATES: That's true. I just wanted just to make the point just so that it's noted.

DR. JEFFCOAT: No, I'm just saying that for the record.

DR. BATES: Um-hum.

DR. JEFFCOAT: That's all. Dr. Jeffcoat. Yes, Judith.

DR. ZELIKOFF: The third paragraph after the box, where it states that taking into account factors such number and size of teeth and respiratory volumes and rates, FDA estimates that the estimated daily dose of mercury in children under age 6 with dental amalgams is lower than the estimated daily adult dose.

I find that difficult to believe and I also think that that should not be included. There's so many scientific points that make it counterintuitive, including, you know, the physiology of a lung, the reduction of metabolizing enzymes in young children, the reduction in antioxidants, the increased breathing rates, so they'd be breathing more in. So I have some difficulty and discomfort with that sentence.

DR. JEFFCOAT: Yes.

MR. ADJODHA: Michael Adjodha, FDA. I think Mr. Watson had just mentioned that we were okay with this slide and --

DR. JEFFCOAT: Yeah.

MR. ADJODHA: -- that we were not going to revisit the information outside of the box --

DR. JEFFCOAT: Okay.

MR. ADJODHA: -- because it all is dependent on what's in the box.

DR. JEFFCOAT: It's all dependent upon --

MR. ADJODHA: Yeah.

DR. JEFFCOAT: -- on suggestion three, two or whatever it was.

MR. ADJODHA: Right.

DR. JEFFCOAT: Don't hold me to the number. Does it have to do with the outside-of-the-box information? That's actually moot? Does anyone else on the Panel --

DR. ISMAIL: I move to adjourn. I move to --

DR. JEFFCOAT: Well, okay.

DR. ISMAIL: Thank you.

DR. JEFFCOAT: I want to thank the Panel, who not only has read extensive information and been here and listened very carefully for 2 days. Nobody was on the phone outside, I have to say, at least that I could see. And they actually carried this information here. So I really want to thank everybody for that.

I want to thank the FDA for answering our questions in preparation to the meeting, for preparing the Panel pack, and for having a very good atmosphere for discussion. And discussion doesn't always mean total agreement.

And I want to ask, Mr. Watson, if you would like to say something?

MR. WATSON: Yes, I would. I just wanted to thank the Panel and especially Dr. Jeffcoat. The FDA really appreciates everyone's input. And

I also want to thank the public speakers and the invited speakers who came. I think your testimonies are very important.

We're going to go back, as I mentioned, and really hit this and hopefully we'll come out with something that everybody can be proud of. Thank you very much.

DR. JEFFCOAT: Thank you, Olga. This meeting of the Dental Products Panel is now adjourned.

(Whereupon, at 5:00 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

NEUROLOGICAL DEVICES PANEL

October 8, 2010

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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TIMOTHY ATKINSON

Official Reporter