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**THE U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
CENTERS FOR DISEASE CONTROL AND PREVENTION**

convenes

**THE NATIONAL VACCINE ADVISORY COMMITTEE  
SPONSORED WORKSHOP ON THIMEROSAL VACCINES**

**DAY ONE - VOLUME I  
AUGUST 11th, 1999**

The verbatim transcript of the Sponsored Workshop on Thimerosal Vaccines held Wednesday, August 11th, 1999, at the National Institutes of Health, Lister Hill Auditorium, Bethesda, Maryland.

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1 across the street, which has a much larger cafeteria  
2 than is in this building.

3 Thimerosal has been used as an additive to a number of  
4 biologics since the 1930s, including some vaccines  
5 routinely recommended for use in young children.

6 Because of multiple doses of vaccine, it is possible  
7 that some children could be exposed to a cumulative  
8 level of mercury that exceeds guidelines for  
9 methylmercury.

10 Nationally and internationally, manufacturers and  
11 regulatory agencies are working to replace or reduce  
12 thimerosal-containing vaccines.

13 The purpose of this workshop is to review the pertinent  
14 data on thimerosal: its use; its potential for  
15 toxicity; and steps that can be taken to increase the  
16 margin of safety, especially during the period of  
17 transition to greater availability of vaccines without  
18 thimerosal or with reduced thimerosal.

19 It's very -- It's important to discuss, as we discuss  
20 these issues, to balance these with the very real risks  
21 of disease resurgence if we have a reduction in vaccine  
22 utilization or a loss of confidence in vaccines.

1 We're a very diverse group of people here today, but  
2 let me say that the primary audience to whom this  
3 information is directed, the members of the Federal  
4 Advisory Committees that relate to vaccines. These  
5 include the National Advisory -- National Vaccine  
6 Advisory Committee that is sponsoring the workshop, the  
7 Advisory Committee on Immunization Practices, the  
8 Vaccines and Related Biologic Products Advisory  
9 Committee, and the Advisory Commission on Childhood  
10 Vaccines.

11 The workshop is convened specifically for the exchange  
12 of information. It is not a policy meeting nor is it  
13 designed to provide advice.

14 I'd like to say a little bit about the format of what  
15 we're trying to do today. The first is, we're going to  
16 talk about thimerosal, why we have preservatives in  
17 vaccines and some of the issues that surround the  
18 inclusion and experience of now over sixty years with  
19 thimerosal.

20 Then we're going to talk about organomercurials, both  
21 thimerosal as an organomercurial-containing additive as  
22 well as organomercurials in general.

1 We're going to end the afternoon talking about  
2 potential disease impact of the diseases that are --  
3 the vaccines that would be primarily affected during a  
4 transition to a reduced thimerosal vaccine supply.  
5 Tomorrow we're going to talk about the transition to a  
6 greater supply of thimerosal-free vaccines in reduced  
7 thimerosal-containing vaccines. We're going to talk  
8 about issues that relate to the manufacturer and  
9 regulatory activities, the European initiative, and  
10 then we're going to talk about the transitional vaccine  
11 options, the flexibility within the recommended  
12 schedule.

13 At that time, we're going to -- we have a number of  
14 groups and individuals who would like to participate by  
15 giving their perspectives on these options. We have  
16 allowed time in that session for others who would like  
17 to give their perspective on this, as well. We didn't  
18 know how much time to allow. We have limited time. We  
19 have a very full agenda for the next couple of days.  
20 So if there are individuals or groups that would like  
21 to give a perspective on this, if they'd put together a  
22 one- or two-sentence summary, we've asked Dr. Modlin,

1       who is going to be our moderator tomorrow, to triage  
2       these and work that last minute changes on the agenda.  
3       And then, finally, many of us feel that  
4 the -- one of the most important parts of this meeting will  
5       occur at the end, which is a discussion of knowledge  
6       gaps that exist.

7       We've tried to ensure a discussion time after each  
8       presentation, and speakers have been asked to limit  
9       their talks to allow five or ten minutes of discussion.

10       To use the microphones, the individual microphones at  
11       your seats -- I've got to read this here, and it's  
12       tough with bifocals -- you need to depress the "Request  
13       to Talk" button, and red and green lights will come on,  
14       and that means that the microphone is on, and then you  
15       depress it again to turn it off, and both lights will  
16       go off. We'll ask our moderators to triage the  
17       questions and also to keep us focused and on time.

18       Dr. Georges Peter, who is Chair of the National Vaccine  
19       Advisory Committee, asked me to extend his sincere  
20       regrets at his inability to be here today and to  
21       express his appreciation to Dr. Klein for serving as  
22       both a convener and rapateur (sic).

1 Dr. Harry Greenberg will be our moderator today. Dr.  
2 Greenberg is the Chair of the VERPAC. Dr. John Modlin  
3 will be our moderator tomorrow, and he is the Chair of  
4 the ACIP. Again, they're going to make every effort to  
5 keep us on time.

6 We are going to develop proceedings from this meeting.

7 Therefore, even though everybody knows you in the  
8 room, if that's the case, please tell us who you are  
9 and your affiliation, so our transcriber will be able  
10 to put that together.

11 So, with no further ado, I will ask Dr. Klein to  
12 convene the meeting.

13 **DR. KLEIN:** Thank you, Dr. Myers. It's a privilege to  
14 be a participant in this very -- what I anticipate will  
15 be a very informative experience for all of us. I  
16 think we start out with a relatively limited base of  
17 information about organomercurials and, particularly,  
18 about concerns for these products in vaccines.

19 The specific issue of thimerosal is one that is -- has  
20 history of about sixty years. Its use as preservative  
21 in biologics and pharmacologic preparations goes back  
22 to the 1930s, and it is present, or has been present,

1 not only in vaccines, but in various cosmetics, contact  
2 lens solutions. So its use as a preservative goes  
3 beyond the specific area of vaccines.

4 Thimerosal is an ethylmercury salt, and it's important  
5 to keep the distinction about the disasters that have  
6 occurred with mercury with which we are familiar from  
7 the paucity of information about any harmful effects of  
8 ethylmercury, but we'll hear more about that.

9 Thimerosal is present in some but not all vaccines.

10 Most of the viral vaccines do not have thimerosal.

11 Both the oral and inactivated polio vaccines do not.

12 Measles/mumps/rubella does not. Varicella vaccine does  
13 not. Rotavirus, hepatitis A, and Lyme disease vaccines  
14 all do not preservatives. They don't have thimerosal.

15 Thimerosal is present in some but not all DTP and DTaP  
16 preparations. Some of the hepatitis immune -- I'm

17 sorry -- amphophilous influenza B, polysaccharide  
18 conjugate vaccine, the benignococcal and pneumococcal  
19 polysaccharide vaccines, as well as hepatitis B. And

20 there will be more discussion about the focus of  
21 changes for hepatitis B vaccine.

22 This product is antibacterial and prevents, as well as

1 may treat, infectious agents that are present in these  
2 various products. The antibacterial activity is  
3 related to release of ethylmercury after spontaneous or  
4 enzymatic breakdown of thimerosal into ethylmercury and  
5 thiosalicylate. It is bactericidal at acidic pH. It  
6 is bacteriostatic and fungistatic at alkaline or  
7 neutral pH.

8 The most frequent adverse events that have been  
9 identified with thimerosal are those of a  
10 hypersensitivity reaction, papular or vesicular  
11 disruptions. Some of the solutions for contact lenses  
12 have caused eye irritations.

13 It is methyl, not ethyl, toxicity that has been  
14 associated with the well-known events in Minamata,  
15 Japan, resulting from the contamination of fishing  
16 waters in the area and the severe consequences for  
17 people in that area.

18 Use of methylmercury has been as a fungicide, and the  
19 mistaken use in preparation of homemade bread rather  
20 than grain for planting in Iraq led to many -- severe  
21 morbidity and mortality.

22 In contrast then, thimerosal is ethylmercury; and to

1 underline, there is no evidence of harm from the  
2 amounts of mercury administered to infants and children  
3 in vaccines.

4 I think what we'll learn from this experience in the  
5 next two days I've categorized in six areas.

6 One, the use of preservatives in vaccines, are they  
7 necessary? Are they necessary for specific products?  
8 Are there are substitutes that can be made if they are  
9 necessary for the thimerosal that is now used?

10 Two, we'll talk specifically about mercury and the  
11 pharmacokinetics and toxicology in animals as well as  
12 some human data.

13 Three, the impact, and there will be considerable  
14 discussion later today on any issues that arise that  
15 may limit public confidence in vaccines and alter our  
16 current success in immunization program.

17 Four, what are the current plans to reduce or eliminate  
18 thimerosal in vaccines?

19 Five, the pragmatic issues about what to do during the  
20 transition from the current roster of vaccines that do  
21 contain thimerosal to a thimerosal-free vaccine,  
22 period.

1 And then finally, a review of appropriate priorities  
2 for research in these areas.

3 So I anticipate an educational experience for all of  
4 us.

5 To begin this morning's program, I'd like to introduce  
6 the moderator for the morning session, Dr. Harry  
7 Greenberg, who is Senior Associate Dean for Research at  
8 Stanford University and Chief of Staff of Research at  
9 the Palo Alto VA.

10 Dr. Greenberg.

11 **DR. GREENBERG:** Thank you, Dr. Klein, and thank you all  
12 for coming. I see my role as sort of the heavyweight,  
13 or bad guy, and I've been advised that I have the  
14 privilege of yanking anybody I want off the stage if  
15 they talk too long. I will tell all the speakers that  
16 there's an incredible little button up here that will  
17 eject you if you go beyond twenty-five minutes. And if  
18 it doesn't function, I will eject you.

19 The purpose, I think Dr. Myers really hit the nail on  
20 the head when he said the main purpose of this meeting  
21 is to get all of us on the same page as far as our  
22 database as to what the issues are here, and I look

1 forward to a very, very informative meeting.  
2 We're ahead of time, and maybe we'll be able to keep  
3 ahead of time during the meeting, but if, by chance,  
4 that doesn't occur, like it never does, I may have to  
5 cut off some of you who I am sure have the most  
6 important question to ask. It is nothing personal, but  
7 I will use my prerogative to keep the meeting on time.  
8 And so, trying to keep it -- keep on schedule, I'd like  
9 to introduce the first speaker, who is Dr. William  
10 Egan, Acting Director, Office of Vaccine Research and  
11 Review at CBER, FDA, and he's going to start off that  
12 first session that we're talking about: Where Are We  
13 Now: A Review of the Data -- Thimerosal in Vaccines.  
14 His perspective is from the FDA.  
15 Bill? First, I'm starting his time. Instruction is on  
16 your time.

17 (LAUGHTER)

18 **DR. EGAN:** Okay. Thank you very much. We'd like to  
19 thank you, Dr. Myers, for the opportunity to come here  
20 and say a few words about preservatives in a FDA  
21 perspective.

22 Let me begin by relating one incident that's described

1 in Sir Graham Wilson's classic book, "The Hazards of  
2 Immunization." It goes:

3 "In January, 1928, in the early stages of an  
4 immunization campaign against diphtheria, Dr. Ewing  
5 George Thomson, Medical Officer of Health at Bundaburg,  
6 in Australia, began the injection of children with  
7 toxin-antitoxin mixture. The material was taken from  
8 an India rubber-capped bottle containing 10 mLs of the  
9 toxin-antitoxin mixture. On the 17th, 20th, 21st, and  
10 24th of January, Dr. Thomson injected subcutaneously a  
11 total of twenty-one children without ill effect.  
12 On the 27th, a further twenty-one children were  
13 injected. Of these children, eleven died on the 28th  
14 and one on the 29th."

15 The death of these twelve children was investigated by  
16 the Royal Commission, and the final sentence in the  
17 summary of their findings reads as following:

18 "The consideration of all possible evidence concerning  
19 the deaths at Bundaburg points to the injection of  
20 living staphylococci as the cause of the fatalities."

21 As Sir Graham Wilson also notes in his book, staph  
22 toxin was very likely also present in the bottle, thus

1 accounting for the rapid deaths of the children.

2 Obviously, the bottle became contaminated on the 24th  
3 of January, the bacteria multiplied, toxin was  
4 produced, and the bacteria then injected into the  
5 children on the 27th.

6 Among the recommendations of the Royal Commission is a  
7 very important one, that biological products in which  
8 the growth of a pathogenic organism is possible should  
9 not be issued in containers for repeated use unless  
10 there is a sufficient concentration of antiseptic to  
11 inhibit bacterial growth.

12 The number of similar examples of bacterial  
13 contamination, either during manufacturing or during  
14 product use, are detailed in Sir Graham Wilson's book,  
15 "The Hazard of Immunization." And, sadly, many  
16 additional examples of the consequences of bacterial  
17 contamination have been revealed since the publication  
18 of that book.

19 However, from these disasters, these and similar  
20 disasters, have arisen the regulations that require  
21 preservatives in multi-dose, multi-entry containers of  
22 biological products. Indeed, if I may offer a general

1 comment, many of the requirements that now exist for  
2 biological products have arisen not from foresight, but  
3 from mishaps.

4 The U.S. Code of Federal Regulation contains a  
5 requirement for preservatives in multi-dose containers.

6 This requirement was placed into the Code of Federal  
7 Regulations in January of 1968, although biological  
8 products had contained preservatives, including  
9 thimerosal, prior to this date. Indeed, Eli Lilly had  
10 thimerosal in their diphtheria toxoid vaccines in the  
11 1930s.

12 Specifically, the CFR states that: "Products in multi-  
13 dose containers shall contain a preservative, except  
14 that a preservative need not be added to Yellow Fever  
15 Vaccine; Polio-Virus Vaccine, live oral; viral vaccine  
16 labeled for use with the jet injector; dried vaccines  
17 when the accompanying diluent contains a preservative;  
18 or to an allergenic product in fifty percent or more in  
19 volume of glycerine."

20 The CFR also requires that a preservative that is used  
21 shall be sufficiently nontoxic so that the amount  
22 present in the recommended dose of the product will not

1 be toxic to the recipient, and in combination used it  
2 shall not denature the specific substance in the  
3 product to result in a decrease below the minimal  
4 acceptable potency within the dating period when stored  
5 at the recommended temperature.

6 The CFR does not specifically address the use of  
7 preservatives in single-dose containers. Currently,  
8 some single-dose presentations contain preservatives.  
9 Some do not. In the past, it was thought that single-  
10 dose containers, like multi-dose containers, should  
11 contain preservatives, the rationale being that the  
12 addition of a preservative during the manufacturing  
13 process or during the filling operation served to help  
14 ensure that the product was free of microbial agents  
15 and their toxins.

16 Indeed, at the International Symposium on Preservatives  
17 in Biological Products held twenty-five years ago, in  
18 San Francisco -- This was under the auspices of the  
19 IABS -- Dr. Edward Seligman, Jr., at that time the  
20 Director of the Bureau of Biologics Division of Product  
21 Quality Control, had the following comment:

22 "Because of the numerous complex processing stages in

1 the manufacture of biological products, good  
2 manufacturing procedures include the addition of  
3 preservatives early in the manufacture of many types of  
4 products to aid in preventing contamination during  
5 production. Even if products are sterilized by  
6 filtration prior to filling into final containers,  
7 contamination during earlier stages can result in  
8 soluble products that alter the purity of the product,  
9 increase toxicity, and result in pyrogens, all of which  
10 cannot be removed without alteration of the product  
11 itself."

12 Now, today, GMPs are viewed differently, and it would  
13 be argued that a well-controlled process does not  
14 require the addition of a preservative to ensure  
15 sterility. However, I think at this point, it's  
16 worthwhile noting that sterility is not an absolute  
17 term. Sterility does not mean zero microbial organisms  
18 in one hundred percent of the containers.

19 Let me show some data that was presented by Koerner and  
20 Kindt from the (inaudible) in Germany at this symposium  
21 twenty-five years ago. Well, this is filling data, so  
22 number of lots that were filled and the percentage of

1 non-sterile filling lots. And with no preservatives in  
2 ampules, 5.6 percent of the lots were found to be non-  
3 sterile. This is using the test that's in the CFR.  
4 For multi-dose containers, somewhat better, 2.2  
5 percent. And even when preservatives were used, if we  
6 look at the ampules, the number of lots that were  
7 rejected went from 5.6 to 4.4 with phenol, to 2.1 with  
8 an organomercurial. In the multi-dose containers, it  
9 went from 2.2 down to 0.3 with phenol and 0.8 with the  
10 organomercurial.

11 While formaldehyde was in there, they rejected  
12 seventeen percent of the lot. This was not  
13 statistically different than the 5.6, the small  
14 numbers. The numbers in parentheses refer to the  
15 number of lots rejected over the total number of lots  
16 that were examined.

17 And even in the -- with no preservatives, with the  
18 multi-dose containers with some residual formaldehyde,  
19 it was the same as no preservative. Formaldehyde does  
20 nothing.

21 The reason I show these data is simply to point out  
22 that even with the preservatives, there was still a

1 number of lots that were rejected because of issues of  
2 stability.

3 Now, today, these numbers are significantly lower, and  
4 if manufacturers would, you know, would do media fills  
5 to test the -- you know, the filling, and we're looking  
6 at numbers like one in ten to the three or one in ten  
7 to the four containers that might have microbial  
8 growth.

9 However, I point this out simply to say that the  
10 numbers will not be zero and the risk of no  
11 preservative will be slightly greater than with the  
12 preservative. No matter how small they are, the  
13 numbers are not zero. There may be some discussion  
14 later on this point.

15 Now, I've spoken for the past nearly ten -- five, ten  
16 minutes about preservatives, but have yet to say what a  
17 preservative is and what precisely we expect a  
18 preservative to do. If I may come back and quote Dr.  
19 Seligman again, he mentioned that the sole reason for  
20 adding a preservative is to protect the recipient.  
21 Thus, a preservative must be able to protect the  
22 recipient from the consequences of inadvertent

1 microbial contamination while at the same time being  
2 nontoxic to the recipient and not denaturing the  
3 product.

4 Sodium azide is a good preservative, but its use in  
5 (inaudible) would not be allowed because of toxicity.  
6 Thimerosal is a good preservative, but not for IPV. It  
7 inactivates the vaccine. Hence, we have the  
8 regulations that I showed before, that a preservative  
9 must be nontoxic and must not denature the particular  
10 substance.

11 But what needs a preservative to do? Obviously, as  
12 I've said, a preservative must prevent the consequences  
13 of inadvertent contamination by microorganisms  
14 introduced during use of the product.

15 However, does this mean that a preservative must be  
16 bactericidal or fungicidal, or is it sufficient that  
17 the preservative assure microbial stasis? And whether  
18 a preservative should be cidal or simply ensure stasis,  
19 we need to ask as well, against what organisms, at what  
20 levels, and if a preservative must be cidal, how  
21 rapidly. These issues are not addressed in the Code of  
22 Federal Regulations.

1 Now, under proper conditions of storage, usually  
2 refrigerated, and with good medical practice, the  
3 extent of potential inadvertent contamination should be  
4 minimal. The number of -- The number of the types of  
5 potentially contaminating organisms is quite large, and  
6 there are long lists in various texts on preservative  
7 and stabilities. And there could be and there has been  
8 considerable argument regarding which organisms a  
9 preservative should be able to exclude. However, if we  
10 look at past examples, past tragedies, that list would  
11 certainly include the staphylococci and streptococci.  
12 Now, preservatives are also discussed in the United  
13 States Pharmacopeia, and the USP regards antimicrobial  
14 preservatives as substances added to dosage forms to  
15 protect them from microbial contamination. They are  
16 used mainly in multi-dose containers to inhibit the  
17 growth of microorganisms that may be introduced  
18 inadvertently during or subsequent to the manufacturing  
19 process.

20 The USP further states that any antimicrobial agent may  
21 exhibit the protective properties of a preservative.  
22 However, all useful antimicrobial agents are toxic

1 substances. For maximum protection to the consumer,  
2 the concentration of the preservative should be  
3 considerably below the concentrations of the  
4 preservative that may be toxic to human beings.  
5 These discussions of a preservative that are in the USP  
6 are thus quite similar to those in the CFR. The USP,  
7 however, does provide a functional definition of  
8 preservative, whereas the CFR does not.

9 I should add also that the USP tests a preservative  
10 only in the original unopened container in which the  
11 product was distributed by the manufacturer. So it's  
12 not a preservative, per se, as an entity, but only that  
13 entity in a specific product.

14 Now, an ample number of examples may be found in  
15 literature wherein a substance at a particular  
16 concentration functions as a preservative, per the USP  
17 definition, for one biological product but fails in  
18 another. For example, a preservative at a -- a  
19 material at a particular concentration may be a good  
20 preservative for a vaccine, but in a blood product or  
21 in serum does not function -- does not function, does  
22 not meet the USP requirements.

1 Now, let me outline briefly the USP definition of  
2 "preservative." It's a functional definition wherein a  
3 specified amount of the product is challenged with a  
4 known quantity -- Actually, 0.1 milliliters of  
5 approximately  $10^5$  to  $10^6$  per ml of the following  
6 organisms, or spores: candida albicans, aspergillus  
7 niger, escherichia coli, staphylococcus aureus, and  
8 pseudomonas aeruginosa, and it specifies the strains  
9 from the American-type culture collection.

10 The test sample is incubated at 20 to 25 degrees, and  
11 the number of viable organisms determined on days 7,  
12 14, 21, and 28. And a preservative is then acceptable  
13 if bacteria are reduced to less than 0.1 percent of the  
14 challenge dose by day 14; yeast and mold remain at or  
15 below the initial inoculum on day 14, and the number of  
16 organisms -- This should be on day 28 -- are the same  
17 or below that on the day 14 level.

18 Now, for bacteria, the USP definition is a bactericidal  
19 one. For yeast and mold, the definition is one of  
20 stasis. Although the choice of challenge organisms  
21 might be argued, most people would agree that the USP  
22 challenge assay is quite stringent in that the

1 challenge doses are much greater than might ordinarily  
2 be expected to occur through inadvertent contamination  
3 during use. Thus, a preservative, as defined by the  
4 USP, provides a large margin of safety.

5 Now, the question may be raised whether the term  
6 "preservative" as used in the CFR is defined as per the  
7 USP. In other words, must we take the USP definition?

8 The preservative that is in the CFR is a preservative  
9 as defined in the USP.

10 The simple answer to this question is no. A material  
11 that does not meet the USP requirements may still be  
12 deemed by CBER to satisfy the CFR requirements for a  
13 preservative. Although a material satisfying the USP  
14 definition will certainly be acceptable as a  
15 preservative, other definitions are possible.

16 However, if a different set of requirements are to be  
17 met -- different organisms, different concentrations,  
18 different times to kill, et

19 cetera -- then the rationale for their use must be presented  
20 to CBER for approval in the products.

21 Now, we're at the workshop today to discuss thimerosal  
22 and its reduction and removal -- well, removal from

1 existing products. This will entail switching to  
2 single-dose vials without preservatives or using  
3 single-dose and multi-dose vials with different  
4 preservatives. Such changes may constitute a change in  
5 formulation of the product. Dr. Baylor, in his talk  
6 tomorrow, will discuss how CBER will handle these  
7 product formulation changes from a regulatory point of  
8 view.

9 A little later in this talk -- in this session, Dr.  
10 Ball from FDA will be discussing the vaccines that  
11 contain thimerosal, the content of thimerosal in those  
12 vaccines, and the guidelines that are now existing  
13 regarding mercury intake, and I believe that Dr.  
14 Plotkin will be following me and presenting some data  
15 on alternative preservatives.

16 Okay. Nineteen minutes, Harry. You got one extra  
17 minute.

18 **DR. GREENBERG:** Thank you, Bill. Stay up here because  
19 we have some time for some questions. I'd like to  
20 thank you for an excellent talk.

21 Can I ask the first question? I assume that thimerosal  
22 or thimerosal --

1 DR. EGAN: Actually, one's used -- one is the term used  
2 in Europe, the other is the term used in the U.S..  
3 They're the same chemical.

4 DR. GREENBERG: Good.

5 DR. EGAN: Next question.

6 (LAUGHTER)

7 DR. GREENBERG: I assume that that fits under the USP  
8 definition.

9 DR. EGAN: Yes.

10 DR. GREENBERG: Okay. Do we have any questions for Dr.  
11 Egan? You have a little mic in front of you that  
12 you're supposed to -- Yes, you're on. Neal, you're  
13 Number 8-A.

14 DR. HALSEY: Two questions, one -- the first one is,  
15 does that USP --

16 DR. GREENBERG: Could you stand up and identify  
17 yourself to the audience?

18 DR. HALSEY: Neal Halsey, John Hopkins University.

19 DR. GREENBERG: Then you can sit down.

20 (LAUGHTER)

21 DR. GREENBERG: I'm learning as we go along here.

22 DR. HALSEY: All right. Two questions. The first one

1 is: Does the USP test, the pharmacopeia test, require  
2 the product to be used -- that preservative to be  
3 tested in the final product, and is this being --

4 **DR. EGAN:** Yes.

5 **DR. HALSEY:** -- because of the -- If you might address  
6 the issue of the contamination of DTP with Group A  
7 strep, and Group A strep is not one of the organisms  
8 which you mentioned back there, but the basis for why  
9 that doesn't work as perfectly as we would like to,  
10 because there are multiple reports of clusters of those  
11 cases, and I have always assumed it was because of the  
12 particular matter that was in DTP that may have played  
13 a role in helping protect it.

14 The second question has to deal with the definition  
15 under the USP and whether it's your understanding in  
16 terms of the safety, and I don't have the words in my  
17 head exactly, but the toxicity for the recipient must  
18 be considerably below that that might be toxic, is the  
19 sort of language that you used. Is your interpretation  
20 of that definition with regard to thimerosal, does the  
21 current concentrations fall within that safety  
22 guideline or they exceed that safety guideline?

1 **DR. EGAN:** Okay. Let me try the first question first.

2 That related to the USP definition about whether it  
3 corresponds to the preservative in the material, and  
4 the answer to that question is yes. So, in other  
5 words, they take the final dosage formulation and then  
6 it's challenged with those five -- those five  
7 organisms.

8 Your second question was --

9 **DR. GREENBERG:** Bill, I --

10 **DR. EGAN:** Yes?

11 **DR. GREENBERG:** Neal, it seems to me that your second  
12 question is the purpose of this meeting. So rather  
13 than, in the first speaker, trying to -- I think maybe  
14 you'd be wise to ask that question at the end of the  
15 meeting.

16 Now, any other questions?

17 **DR. McINNUS:** Pamela McInnus, NIAID. I'd like some  
18 clarification following this first talk: Are we moving  
19 forward with this workshop on the basis that available  
20 data do support the decision to reduce and eliminate  
21 thimerosal? Is that up for discussion at all, or is  
22 that decision made and is nonretractable?

1       **DR. EGAN:**   Okay --

2                               (LAUGHTER)

3       **DR. EGAN:**   Well, let me speak for myself personally,  
4       and I believe that we -- you know, we, i.e., FDA, have  
5       made that decision to -- whenever possible, to  
6       eliminate thimerosal from products.  We have asked  
7       manufacturers and sponsors in the development of their  
8       products to develop them without thimerosal; and if  
9       they're not able to do that, to specifically explain  
10      why.

11      So the use of thimerosal as a preservative is no long  
12      the default option.

13      And, you know, we did send out a letter earlier -- sent  
14      out a letter this summer again asking manufacturers and  
15      sponsors for their plans to reduce -- reduce or  
16      eliminate thimerosal in their products.  So I think  
17      that's where we're heading.  I'm not sure where the --  
18      this workshop will be headed.

19      **DR. GREENBERG:**  Pam, I would like to say, also I think  
20      your question, at least for me, who is less well-  
21      informed than many of you, that part of the purpose of  
22      this meeting is to get a database in front of all of us

1 at the same time and then potentially to re-evaluate  
2 decisions that were made, but at least to have a very  
3 broad and deepening airing of available information so  
4 that your question can be answered in a scientific way.  
5 Any other questions? In the back?

6 **DR. CORDERI:** José Corderi, CDC. Bill, what  
7 preservatives are now available, other than thimerosal,  
8 that would meet the USP definition for preservative?

9 **DR. EGAN:** For the common childhood vaccines, the only  
10 one that I'm aware of that -- in the product  
11 formulations that is used is 2-phenoxyethanol.

12 **DR. CORDERI:** Any others?

13 **DR. EGAN:** Not that I'm aware of in the childhood  
14 vaccines. In anthrax, for example, there's  
15 benzalkonium chloride, which is an ammonium salt. I  
16 don't think we have phenol in any of the vaccines  
17 anymore, but I would have to go back and check that  
18 specifically for all of them.

19 **DR. GREENBERG:** Other questions?

20 (NO RESPONSE WAS HEARD)

21 **DR. GREENBERG:** If not, I'd like to thank you, Bill.  
22 And we are -- I'm going to get all of you home early.

1 The next speaker is Dr. Stanley Plotkin, who is now the  
2 Medical and Scientific Advisor to Pasteur Mérieux  
3 Connaught, and he is going to be talking to us about  
4 preservatives, the manufacturer's perspective.

5 **DR. PLOTKIN:** Well, Harry, first of all, let me stress  
6 that this talk does not represent the view of the  
7 entire manufacturing industry. I have not canvassed  
8 manufacturers' views and I would not presume to speak  
9 for them. This is my view, reflecting experience both  
10 in academic vaccine development and as a consultant to  
11 one manufacturer.

12 Indeed, after I am done speaking, manufacturers in  
13 general, and Pasteur Mérieux Connaught, in particular,  
14 may choose to disavow what I have to say.

15 (LAUGHTER)

16 **DR. PLOTKIN:** Vaccine manufacturers -- Vaccine  
17 manufacture is, as it should be, a highly regulated  
18 industry, designed to produce safe and effective  
19 vaccines. Like many of you, I first became aware of a  
20 perceived crisis with respect to thimerosal at the time  
21 of the ACIP meeting late in June through communications  
22 concerning a meeting held at the FDA.

1 Subsequently, there was an urgent meeting called by the  
2 American Academy of Pediatrics on June the 30th, at  
3 which it was announced that there was an emergency  
4 based on concerns about the presence of thimerosal in  
5 pediatric vaccines.

6 This was puzzling, as thimerosal has been used for at  
7 least fifty years, and, therefore, I expected to hear  
8 new data concerning its effects. At the end of the AAP  
9 meeting, I was largely disappointed. Nevertheless,  
10 there were some salient points that emerged from that  
11 meeting.

12 First, that the FDA and the EPA were apparently not in  
13 agreement with each other in regard to the guidelines  
14 for mercury exposure.

15 Second, that if the EPA guidelines were assumed to be  
16 preferable, some infants might receive a combination of  
17 vaccines with sufficient mercury to exceed those  
18 guidelines.

19 Third, that a small uncontrolled study, published only  
20 in abstract, showed significant blood levels after  
21 neonatal hepatitis B vaccination.

22 Thus, three changes had taken place with respect to the

1 use of thimerosal. First, the perception of danger,  
2 experience with methylmercury exposures, and increasing  
3 environmental concerns led the EPA to issue strict  
4 guidelines with respect to mercury exposure. These  
5 guidelines were designed to provide a margin of safety  
6 based on the available data concerning toxicity of  
7 methylmercury.

8 As various guidelines had been proposed, one could  
9 calculate differently the allowable mercury ingestion,  
10 and Leslie Ball, I believe, will later give these  
11 different calculations.

12 So here we have a situation of apparent disagreement  
13 between agencies and where industry may have been  
14 following a guideline that could be abandoned or  
15 altered.

16 It is important to understand, as I learned, what is  
17 meant by a guideline. The statement on this slide is  
18 from the recent EPA report which explains how the  
19 guideline was chosen. Now, I don't know that I should  
20 read this, but the point is that calculations were  
21 based on a hair concentration conversion to blood  
22 levels, and these were a blood level of 11 -- I'm sorry

1 -- of 44 micrograms per liter of blood; hair  
2 concentration you can read; and then an uncertainty  
3 factor of 10 was used to derive the acceptable dose,  
4 which was thought to be safe. It was stressed that  
5 this reference dose is likely to be without appreciable  
6 risk of deleterious effects during a lifetime.  
7 Exceedence (sic) does not mean that risk will be  
8 present.

9 There is an impression of a certain arbitrariness in  
10 the choice, but, of course, a choice must be made. All  
11 of us would like more data. And as science advances,  
12 we must be prepared to change the regulations in  
13 recognition of new data. I trust that we shall see  
14 these new data later in this meeting.

15 The second change is the increasing number of licensed  
16 vaccines recommended for infants. While some of us  
17 perceive that as a good thing, the concern is that this  
18 development may be associated with an accompanying  
19 increase and exposure to thimerosal. I would point  
20 out, however, that thimerosal containing DTaPs have the  
21 same concentration of thimerosal as whole cell DPTs, so  
22 there was no change there.

1 In single-dose presentations, HIB vaccines do not  
2 contain thimerosal, and IPV does not contain  
3 thimerosal. So the only significant addition is  
4 hepatitis B vaccine.

5 The third change, indeed, involves the hepatitis B  
6 vaccine, which we all know is recommended in infancy as  
7 the best way of preventing later infection, cirrhosis  
8 and liver cancer, as has been amply proved in other  
9 countries. The birth dose was recommended as a way of  
10 reducing the number of injections in two- four-, and  
11 six-month-old children, which is itself caused by the  
12 problems that few combination vaccines have been  
13 licensed in this country, and that some of others may  
14 not have been screened for hepatitis B infection during  
15 pregnancy.

16 However, and I will -- Well, however, routine neonatal  
17 vaccination of premature infants was never recommended.

18 The Redbook recommendation here is that infants be  
19 allowed to reach two kilograms of weight before being  
20 vaccinated against hepatitis B, unless their mothers  
21 are hepatitis B carriers.

22 Let me now touch briefly on the data that formed the

1 basis of concern regarding thimerosal. I must start  
2 with a disclaimer that I am certainly not a  
3 toxicologist and would never presume to give an opinion  
4 concerning acceptable levels of mercury. However, I do  
5 have a fair amount of experience in evaluating  
6 scientific evidence.

7 Well, first of all, there are apparently no data to  
8 show that ethylmercury in the concentrations normally  
9 used in vaccines is harmful to infants. The available  
10 data concern methylmercury, and we are asked to  
11 extrapolate the metabolism and toxicity of the former  
12 from the latter, which, on the face of it, introduces a  
13 scientific uncertainty.

14 Second, with respect to methylmercury, it appears that  
15 there are only two large epidemiologic studies  
16 concerning methylmercury exposure, both occurring after  
17 eating fish, and they are in disagreement. The study  
18 in the Seychelles was reassuring in that chronic  
19 exposure of mothers to more mercury than is present in  
20 vaccines was not followed by abnormalities in children.

21 Whereas, in the Faroe Islands, perhaps because of  
22 binge eating of pilot whales or because of concomitant

1 ingestion of PCBs, subtle effects in learning  
2 correlated with blood levels of mercury. The blood  
3 levels, just to remind you, were on the order of 23  
4 micrograms per liter, with an interquartile range of  
5 13.4 -- It's a mistake on the slide -- to 41. The mean  
6 was 22, as I said, and 75 percent of infants had cord  
7 blood levels over 13 micrograms. Also noteworthy is,  
8 it appeared to me, that the hair mercury levels in the  
9 mothers were similar to those in the Seychelle study.  
10 So no data have been produced to suggest that  
11 vaccinated children have suffered from thimerosal  
12 toxicity aside from the allergic reactions already  
13 mentioned.

14 Admittedly, the effects found in the Faroe Islands  
15 exposure to methylmercury are subtle and might be  
16 missed by passive reporting. At least, however, one  
17 epidemiologic study done in the United Kingdom  
18 comparing scholastic achievement in pertussis-  
19 vaccinated children versus unvaccinated children, as  
20 quoted in the IOM report on adverse reactions to  
21 pertussis vaccine, show that vaccinated children were  
22 doing better in school, an effect that was attributed

1 to their parents being smarter.

2 (LAUGHTER)

3 **DR. PLOTKIN:** I mentioned -- It's true. I mentioned  
4 previously the study reported in abstract for memory in  
5 which blood levels of mercury were measured before and  
6 after neonatal hepatitis B vaccination in five full-  
7 term infants and fifteen premature infants. The post-  
8 vaccination blood levels averaged 7 micrograms in very  
9 low birth weight infants, compared to 2 to 3 micrograms  
10 in full-term infants. The mean gestational age of the  
11 premature infants is given in the abstract as 25 weeks.

12 This would mean the infants were mostly below a  
13 thousand grams in weight and should not have received  
14 the vaccine in the first place.

15 However that may be, a few percent of those prematures  
16 had peak blood levels in the range of cord bloods  
17 associated with learning defects in the Faroe Islands  
18 study. No pharmacokinetics follow-up was done, but the  
19 Emory data would seem to reinforce the earlier  
20 recommendation, not to vaccinate premature infants of  
21 very low birth weight.

22 Plus, there seems to be a paucity of data in the

1 literature to show that infants receiving ethylmercury  
2 accumulate mercury in excess of infants who are simply  
3 exposed to mercury in the environment.

4 Now, what are the responses of the manufacturers to  
5 this situation? First, well, it should be recalled --  
6 And Dr. Egan has already well covered this -- why  
7 thimerosal was introduced into vaccines in the first  
8 place -- I don't think I need to repeat that -- and it  
9 was chosen indeed because it is the best preservative  
10 available.

11 Many chemicals have been tested, and on the next slide  
12 we see a short list of the favorite ones: 2-  
13 phenoxyethanol, benzyl alcohol, phenol, cresol.

14 Each preservative must pass tests prescribed by the  
15 U.S. or European Pharmacopeia, as Bill Egan has already  
16 stressed. And he already pointed out that, although in  
17 real life situations, the preservative simply has to  
18 keep organisms from growing. When tested for  
19 regulatory approval they must show an ability to  
20 decrease the number of viable bacteria.

21 Now, I just wanted to show a few slides on comparisons.

22 Here we see a study that was done in the U.S. in 1981

1 in which we see that thimerosal actually in this test  
2 failed against staph aureus, failed against the USP  
3 criterion. 2-phenoxyethanol also failed against e.  
4 coli. In this particular test, phenol was the best.  
5 Two more recent studies done in Europe gave the  
6 following results. On these slides, "A" means  
7 fulfilling the Pharmacopeia's requirement, "B" means a  
8 slower killing effect than is stated in the  
9 Pharmacopeia, and "C" means stasis. "Inc" is  
10 incomplete.

11 So we see here in this comparison that thimerosal was  
12 the best. 2-phenoxyethanol mixed with formol was next,  
13 and let's say phenol and 2-PE were more or less the  
14 same.

15 And another comparison done by another manufacturer  
16 again shows thimerosal to be the better of the three,  
17 the best of the three, when you look at the As, Bs, and  
18 Cs.

19 Undoubtedly, new preservatives, or combinations of  
20 preservatives, are under study, but any sudden decision  
21 to eliminate thimerosal would create a number of  
22 potential problems. The first concern is that, at

1 least temporarily, vaccine available would be disturbed  
2 and vaccination delayed or omitted.

3 If physicians or state public health authorities insist  
4 on immediate access to thimerosal-free vaccines, chaos  
5 will ensue. This is not a commercial issue. Each  
6 manufacturer will have gains and losses in terms of  
7 marketshare. The overall loss is to the vaccine -- is  
8 to vaccination programs.

9 Second, there is the risk that substitute preservatives  
10 will not be as compatible with the vaccines or have  
11 less antimicrobial activity and, therefore, lead to an  
12 increased possibility of accidents.

13 In the absence of preservatives, filling of vaccine  
14 vials must depend more on aseptic filling. Although  
15 the technology for aseptic filling grows more and more  
16 sophisticated, as illustrated on this slide, which  
17 shows a filling apparatus in which the operator  
18 operates in a sterile atmosphere through these  
19 portholes -- although, as I say, this technology gets  
20 more and more sophisticated, it must be admitted that  
21 the absence of a preservative deprives us of a safety  
22 net to maintain sterility in later use.

1 Fourth, as thimerosal participates in the inactivation  
2 and detoxification of Bordetella pertussis in whole  
3 cell DTP, elimination of thimerosal would require  
4 reformulation and re-evaluation of the product.

5 Fifth, as influenza vaccine requires rapid production  
6 of large amounts of vaccine, elimination of a  
7 preservative will shift filling to single-dose vials  
8 and may slow or reduce influenza vaccine production.

9 Finally, if manufacturers must choose between preparing  
10 single-dose vaccines without preservatives and multi-  
11 dose vaccines with preservatives, thimerosal or other,  
12 in general, they are likely to privilege single doses  
13 and therefore reduce the availability of multi-dose  
14 vaccines. The effect on vaccination in the developing  
15 world may be dramatic, as I am sure John Clements will  
16 discuss. In the United States, we should not forget  
17 the effects of loss of multi-dose preservatives and  
18 multi-dose forms on the function of public health  
19 clinics and on the cost of vaccines.

20 The immediate response of manufacturers to this crisis  
21 atmosphere will be the usual one. They will respond as  
22 fast as possible to a perceived public health and

1 consumer demand. In this case, for thimerosal-free  
2 vaccine. As I understand the situation, HIB single-  
3 dose and IPV vaccines are already free of thimerosal,  
4 and hepatitis B vaccines free of thimerosal will soon  
5 be brought to the FDA for approval. DTaP is a mixed  
6 bag, but the manufacturers who use thimerosal will seek  
7 to bring single-dose preparations without preservatives  
8 to the FDA within months.

9 Much will depend on the attitude of the FDA regarding  
10 evaluation of existing data. For example, if removal  
11 of a preservative is considered to potentially alter  
12 stability, there will be delays while real-time  
13 stability studies are undertaken by manufacturers and  
14 then the results reviewed by the FDA. And, of course,  
15 we're looking forward to what Norm Baylor has to say  
16 tomorrow.

17 It is interesting that European regulatory authorities  
18 met to discuss this issue in April of this year, as  
19 many of their vaccines also contain thimerosal. A  
20 working group on thimerosal formed by the European  
21 Medicines Agency issued documents on the subject. Two  
22 of their statements are excerpted on the next slides.

1 As you can read: "For vaccination in infants, the  
2 use of vaccines without thimerosal should be  
3 encouraged. However, in order not to jeopardize  
4 vaccine supplies and immunization programs, it is  
5 advisable to introduce requirements for the elimination  
6 of organomercurials in vaccines on a gradual basis."

7 And another excerpt, the group concluded that  
8 thimerosal should not be banned from medicinal  
9 products; however, taking into account the identified  
10 and theoretical risks, precautionary measures should be  
11 considered. And the most desirable alternative they  
12 mention is preservative-free formulations.

13 It is important to stress that until now European  
14 countries that also used neonatal hepatitis B  
15 vaccination, such as France, Germany, and Italy, have  
16 not changed their recommendations. That includes  
17 Spain, which, like the U.S., recommends universal  
18 neonatal hepatitis B vaccination.

19 So, in summary, what is the manufacturers' view, in  
20 quotes, of the situation as interpreted by me. Frankly  
21 -- And I think it is important to be frank early in  
22 this meeting to promote a useful discussion -- I think

1 that FDA did not give manufacturers sufficient warning  
2 that thimerosal is no longer acceptable, that panic  
3 entered into the deliberations of the AAP, and that CDC  
4 was partly handcuffed by regulations that prevented  
5 adequate consultation with the ACIP.

6 The published evidence that the thimerosal contained in  
7 vaccines is dangerous is unconvincing. Nevertheless,  
8 manufacturers, like everyone else, would prefer to have  
9 a less controversial preservative. Many vaccines  
10 currently sold do not contain thimerosal. And even in  
11 the absence of any regulatory changes, new vaccines  
12 will not be manufactured with it. Yet, it remains the  
13 most active preservative and no equivalent substitute  
14 is available. Political concerns aside, it may be  
15 justified to keep in some vaccine formulations,  
16 particularly those in multi-dose preparations.

17 Beyond the factual scientific issues, the process of  
18 decision in this matter has been flawed. This meeting  
19 should have taken place before a public health decision  
20 or a public announcement was made. There should have  
21 been adequate consultation and discussion.

22 This point of view probably gives offense to some, and

1 I'm sorry that this should be the case as my remarks  
2 are not directed against any person in particular.  
3 Reasonable people may disagree on all of these points,  
4 and I, for one, am prepared to modify my opinion based  
5 on data displayed later in this meeting. However, so  
6 far, manufacturers have seen no evidence for a clear  
7 and present danger, but, rather, a rush to judgment.  
8 At the earlier private meeting called by the AAP, I  
9 tried to recommend to the participants a bit of what  
10 the French call "Sang-Froid." I found it difficult to  
11 give an adequate English translation of the term, but,  
12 recently, I came across the French definition given by  
13 Denis Diderot in the 18th century.  
14 He wrote: "Sang-froid, that quality so necessary to  
15 those who govern, without which one would rarely apply  
16 justly the means to the circumstances, without which  
17 one would lack presence, presence of mind; sang-froid  
18 which submits the activity of the soul to reason and  
19 which preserves one, in every event, from fear, from  
20 frenzy, and from precipitation."  
21 I believe we could all benefit from such dispassionate  
22 reflection. Thank you.

1 (APPLAUSE)

2 **DR. GREENBERG:** Thank you, Stan. That was an  
3 interesting talk. We now can take some questions.

4 **DR. ENGLER:** Dr. Engler from Walter Reed. I was  
5 wondering if in those discussions there was any  
6 consideration of the hundreds of children and adults  
7 who between the '60s and until 1981, when intravenous  
8 gamma globulin became available, received weekly or  
9 every two weeks, 10, 15, 30 cc's of intramuscular gamma  
10 globulin, and in my calculation there's probably a  
11 significant cluster of a couple hundred patients or  
12 more who have received 10,000 milliliters of gamma  
13 globulin, which is probably more than three logfolds,  
14 if not four, more than what are given in standard  
15 childhood immunizations, and that does contain  
16 thimerosal.

17 As far as I'm aware, there's only two cases, and these  
18 are patients who had received this in excess of twenty  
19 years in these kinds of doses who developed some  
20 cerebelli ataxia secondary to accumulated mercury  
21 toxicity. Now, the incident is a separate issue,  
22 certainly, in regards to also the difference in the

1 immune system of the infant from older children or  
2 adults, but in other age groups separate from infants,  
3 that seems to be overwhelming data in terms of the  
4 safety to support some of what you're suggesting.

5 **DR. PLOTKIN:** Yes, thank you. I would agree that in  
6 looking over the literature, as far as I've seen, the  
7 only instances of acute thimerosal toxicity have been  
8 where a gross error was made, I think, in the use of  
9 chloramphenicol and, otherwise, the literature show  
10 conspicuous absence of acute toxicity.

11 But to be fair, as you pointed out, of course the issue  
12 here has focused on the very young infant and the  
13 effects on the central nervous system of the very young  
14 infant.

15 **DR. GREENBERG:** In the back? Could you identify  
16 yourself?

17 **INAUDIBLE SPEAKER:** Stan (inaudible) from Merck. You  
18 covered the other chemical, but did you run across any  
19 studies using radiation as a preservative?

20 **DR. PLOTKIN:** The question that Stan is asking is the  
21 use of radiation as a preservative. That's a good  
22 question. I must admit ignorance. I have not seen

1 those studies. I imagine that under some circumstances  
2 it might be possible, although, with particulate matter  
3 in vaccines, I think there could be some issues about -  
4 - about sterilization and, of course, the effects of  
5 radiation on the active product. So the short answer  
6 the your question is no.

7 **DR. BAYLOR:** I just wanted to add what the real issues  
8 --

9 **DR. GREENBERG:** Identify yourself, please?

10 **DR. BAYLOR:** Oh, I'm sorry. I'm Norman Baylor. I'm  
11 with the CBER Office of Vaccines.

12 The real issue is going in and out of that vial. To  
13 produce the vial, a final fill, that's sterile, that's  
14 not really a problem. But going in and out of that  
15 vial, that wouldn't address that problem.

16 **DR. GREENBERG:** Any other questions?

17 (NO RESPONSE WAS HEARD)

18 **DR. GREENBERG:** Well, Dr. Plotkin had a pretty  
19 controversial talk there. You folks aren't rising to  
20 the bait.

21 (LAUGHTER)

22 **DR. PLOTKIN:** I'm glad to be able to get off the podium

1 and still in one piece.

2 **DR. GREENBERG:** The last speaker before the coffee  
3 break is Dr. C. John Clements, from the Expanded  
4 Program on Immunization, Vaccines, and Other Biologics  
5 at the WHO, and the title of his talk will be  
6 "Preservatives in Vaccines: The Global Perspective."  
7 So he will encompass everything.

8 **DR. CLEMENTS:** Good morning, ladies and gentlemen.  
9 First of all, I want to thank the organizers for  
10 inviting me to come and speak. It's a great privilege  
11 to be here in Washington.

12 Before I actually start the presentation, I want to  
13 acknowledge that in assembling some of the materials  
14 for this I was helped by a colleague of mine, Gary  
15 Schatz, who is a consultant that has been working with  
16 us from CDC and who tragically was killed in a road  
17 traffic accident last Monday. I just want to  
18 acknowledge his contribution to this.

19 As I speak to you this morning, I want you to think of  
20 me both as somebody speaking from a global perspective  
21 from WHO, but also as an advocate for a hundred million  
22 such children as this every year. This young gentleman

1 is sitting in a cardboard box with a hole cut for his  
2 legs and he is very interested in what we're going to  
3 say this morning.

4 As you can see from this molecular description of  
5 thimerosal, it's the mercury which is the pride and the  
6 downfall of this gentleman, and we can all agree, I  
7 think, right away, that the mercury here is not what we  
8 want in preservatives. There's ample evidence that it  
9 is an undesirable molecule which is taken in by the  
10 human through food and drink and pharmaceuticals and  
11 vaccines. In general terms, we're without hesitation  
12 in saying we don't want it, and that is a strong basis  
13 for further action. However, I think we need to  
14 examine the issues a little bit more.

15 And I must say that I'm delighted being third in a row  
16 of three, and I hope you'll find that what I have to  
17 say is very synoptic with the previous two speakers. I  
18 make no apologies for covering similar ground, although  
19 I hope you'll remember my friend from Africa as we  
20 speak. And I keep pressing the wrong key. Never mind.  
21 Okay. The United States has gone through its due  
22 process to identify a problem and take action to remedy

1 it. However, there is a knock-on effect which the rest  
2 of the world must bear as a consequence. And what I  
3 want to do is to draw out in the next few minutes some  
4 of these consequences for you and examine the knock-on  
5 effect. And I want to really say how privileged I am  
6 to be here, and I feel that I'm looking over your  
7 shoulders as you make -- go through this discussion and  
8 make some of these decisions.

9 But also, I'm looking over your shoulder anxiously  
10 because there is an knock-on effect, and I want to be  
11 really sure that each one of you involved in these  
12 decisions understands fully some of the implications of  
13 those knock-on effects.

14 Like Stan, I'm concerned with the scientific process  
15 which has gone on to date. There is a lack of  
16 agreement about the safe cutoff levels for mercury and  
17 there's a variance between the control bodies in the  
18 United States, and certainly between WHO, as to what  
19 those levels should be. And the infant maximum intake  
20 level has been extrapolated only.

21 As far as toxic effects go, it's not clear what levels  
22 of exposure to mercury in the fetus, the neonate, and

1 the infant are harmful. We know that there are harmful  
2 levels, but we certainly don't know at what point we  
3 have to be concerned.

4 Now, what does WHO say about this? Well, if we look at  
5 the most authoritative voice that I can find, the 33rd  
6 Report of the Joint FAO/WHO Expert Committee on Food  
7 Additives, JFOA, pronounced on this in 1989. The  
8 committee confirmed the previously recommended the  
9 provisional tolerable weekly intake of 200 micrograms  
10 of methylmercury. That is equivalent to 3.3 micrograms  
11 per kilo of bodyweight for the general population, but  
12 noted that pregnant women and nursing mothers are  
13 likely to be at greater risk from adverse effects of  
14 methylmercury.

15 And I should point out that the discussions which have  
16 gone over the last two or three months really suggest  
17 that possibly we should be looking at a five-fold lower  
18 cutoff point for pregnant women and nursing mothers in  
19 order to protect the fetal brain.

20 And even though the JFCA committee that met in Rome in  
21 June was aware of the issues regarding thimerosal, they  
22 were not in a position to offer any stronger guidelines

1 regarding cutoff levels for pregnant women and didn't  
2 even trespass into the dark waters of recommending  
3 levels for infants.

4 So the figures that I've been able to get hold of,  
5 then, are for WHO 3.3, for FDA 2.8, and for EPA 0.7  
6 micrograms per kilo bodyweight. But I do stress that  
7 WHO recommendations are based on the adult level and  
8 make no special concessions for pregnant women or  
9 infants.

10 A question already asked: Do we need preservatives in  
11 vaccines? And the way that things are going in the  
12 United States, there's the clear possibility that as  
13 you move to monitor those preparations then there may  
14 be a possibility that they are not needed. However,  
15 this is not the case for the majority of the world.  
16 And in tests that we've undertaken recently in  
17 vaccines, it is clear that the lack of preservatives  
18 pose a serious threat to the integrity of multi-dose  
19 vials which have already been opened and penetrated by  
20 at least one needle through the cap.

21 These lists vary a little bit depending on who's  
22 presenting, but I think we're fairly consistent in

1 identifying some alternatives to thimerosal. 2-  
2 phenoxyethanol is -- looks like the forerunner, but we  
3 have limited information on comparative effectiveness.

4 Formaldehyde, cresol, possibly others. Phenol, I  
5 should draw your attention to, in the WHO regulations,  
6 is not permitted any longer.

7 If thimerosal is not available, what alternative  
8 strategies are there for developing countries? Well,  
9 we can move to a mono-dose vial without preservatives  
10 or we can seek a replacement to the preservatives. But  
11 as is already pointed out by Stan, there are serious  
12 consequences for both options. The product must be  
13 reformulated, new clinical data must be presented, and  
14 new submission for license must be made, and for  
15 vaccine supplied through UNICEF, then a special  
16 WHO/UNICEF approval must be processed. All in all, a  
17 long time interval before availability of either of  
18 these alternatives.

19 You've heard already, and you'll hear I know in a lot  
20 more detail, how the regulatory bodies in the United  
21 States go through their debates. In terms of WHO, we  
22 have an Expert Committee on Biological Standardizations

1 which meets regularly, which is composed of outside  
2 experts. Although it is hosted by WHO, it is not an  
3 internal committee, it is an external committee, and it  
4 results in WHO producing WHO technical report series,  
5 which I've already quoted from once.

6 Expert Committee on Biological Standardizations, ECBS,  
7 what does that say about DPT and thimerosal?

8 "If the vaccine is to be dispensed into multi-dose  
9 containers, a suitable antimicrobial preservative shall  
10 be added. The amount of preservative in the final bulk  
11 shall have been shown to have no deleterious effect" --  
12 Never put that on a slide if you have the say it in  
13 public --

14 (LAUGHTER)

15 **DR. CLEMENTS:** -- "on the toxoid or on any other  
16 vaccine components with which the toxoid may be  
17 combined, and to cause no unexpected adverse reactions  
18 in humans. The preservative in its concentration shall  
19 be approved by the national control authority and don't  
20 include phenol."

21 The other vaccine that we're particularly concerned  
22 about is hepatitis B, and the ECBS says about that:

1 "Each final bulk or final lot shall be tested for the  
2 presence of preservative. The method used and the  
3 permitted concentration shall be approved by the  
4 national control authority. The most common  
5 preservative used for hepatitis B is thimerosal," and  
6 then it goes on to describe the analytical methods.  
7 So, in summary, through the expert committee at WHO is  
8 saying that the task of the  
9 preservative -- the task that the preservative is designated  
10 for -- In other words, to be antimicrobial -- must be  
11 defined and fulfilled.  
12 Again, as Stan has already pointed out, it must not  
13 damage the vaccine in any way, like thimerosal and IPV,  
14 and it must not damage the human recipients, although  
15 that is not spelled out how. The level is set not by  
16 WHO but by the national control authorities.  
17 Now, what implications has all this to do for the  
18 global supply of vaccines? Since Stan has begun to  
19 open up this discussion, I need to just clarify for  
20 some of you who may not be familiar with it, the  
21 majority of the world, particularly developing  
22 countries, looks to three main sources to get their

1 supply of vaccines.

2 The first is the local producer, and that may surprise  
3 some of you who are not familiar with this subject;  
4 secondly, UNICEF-supplied vaccines; and thirdly, they  
5 may go directly to the manufacturer and buy directly  
6 through them.

7 And if you look at this graph, the red at the top is  
8 the local production. I'm sorry I don't have more up-  
9 to-date information to show you, but the trend has  
10 continued where a large proportion of the world's  
11 vaccines are produced in-country and consumed in-  
12 country.

13 If you look at this description of DPT sources by WHO  
14 region, you can see that in the Eastern/Western Pacific  
15 Region and the Southeast Asia Region, a vast proportion  
16 of the vaccine is made locally and consumed locally.

17 We'll discuss the implications in a moment.

18 And for hepatitis B, many countries in the developing  
19 world have HBV transmission by the neonatal route. In  
20 other words, the first week, first two weeks of life  
21 are crucial in protecting the infant; and if there is  
22 no birth dose of hepatitis B given, then there is

1 likely to be transmission of the virus. And this means  
2 that without a birth dose in China, between 10 and 15  
3 percent of all births are likely to result in chronic  
4 infection.

5 What immediate impact on developing countries would  
6 there be if thimerosal were removed from vaccines? As  
7 Stan has already said, existing suppliers would be  
8 unable to supply such vaccines and supplies would  
9 rapidly dry up.

10 Locally-produced vaccines, and remember I've identified  
11 them as being a major source in developing countries,  
12 would be unable to substitute for this preservative.  
13 Local production would either stop or -- I'm not sure  
14 whether it's worse or about the same level of  
15 significance, but they might turn to producing without  
16 the preservative.

17 We've mentioned another strategy of moving to mono-dose  
18 vial preparations, but at the moment, basically all  
19 vaccines in developing countries are drawn from multi-  
20 dose vials.

21 The cold chain could not cope with a five- to twenty-  
22 fold increase in volume which would be resulting from

1 this. It would double the cost of the cold chain, and  
2 result in a cold chain costing around half a billion  
3 dollars a year. There would be a six- to ten-fold  
4 increase in vaccine prices for these countries, which  
5 could not be borne by them. Even if there was a switch  
6 to mono-dose, those products still need relicensing.  
7 The one hope in the dark tunnel at this moment in this  
8 scenario is that we are watching the development of a  
9 pouch-and-needle hepatitis B delivery system in its  
10 field trials, and there is at least the possibility  
11 that that will fill a niche as being a disposable  
12 single-dose delivery system.

13 What happens -- The alternatives open to developing  
14 countries. They could obtain vaccine through their  
15 regular UNICEF supply with a new preservative if a new  
16 preservative became available. They could purchase  
17 directly from industrialized countries. They could use  
18 locally-produced vaccine, or they could use vaccine  
19 which is imported in bulk and filled locally, or they  
20 could switch to mono-dose with no preservatives.  
21 And what about the time and the impact of these  
22 decisions they would make? If they waited for a

1 preservative to be introduced into UNICEF vaccines,  
2 that is going to be a long wait. If they purchase  
3 directly from industrialized countries, not only do  
4 they have the wait, but they will certainly have an  
5 increased cost. If they rely on locally-produced  
6 vaccines, they have to try and obtain the new  
7 preservative, perhaps under license, again a long wait  
8 and an increased cost. If they go for local filling  
9 from bulk purchased overseas and the license, there's a  
10 long wait and an increased cost. And if they switch to  
11 mono-dose, it may be relatively quick, but it will be  
12 far too expensive, both in terms of purchasing the  
13 vaccine and in managing the cold chain.

14 Now, there may be some discrepancy in the time sequence  
15 that I put up here. It's the best we could come up  
16 with in WHO on a sort of Gallup Poll basis, and this  
17 isn't something that you should take as finite, but it  
18 gives you some feel. To find a new preservative -- If  
19 a new preservative is found, there's no guarantee, but  
20 between one and five years. Clinical trials, another  
21 two years. Licensing, a year if it's put on fast  
22 track. To reformulate an existing vaccine to a mono-

1 dose would probably take around one year.

2 In summary, then, my Executive Director, Michael  
3 Scholtz put out a press release a few weeks ago: WHO  
4 will continue to recommend thimerosal-containing  
5 vaccines. We see no reason for changing that given the  
6 present amount of information and the scientific  
7 debate. Mono-dose hepatitis B vaccine will continue to  
8 be administered in the birth dose and all the other  
9 doses from multi-dose vials. At this point, there is  
10 no option about using mono-dose. Although, as I said,  
11 a light in the end of the tunnel is the patch-and-  
12 needle device.

13 And as I indicated already that mercury is a highly  
14 undesirable chemical to have in biological products  
15 anyway, and we are determined to work with industry and  
16 regulate the authorities to eliminate thimerosal.

17 One thing I've observed doing this over the last few  
18 months is a concern, and I asked the question: Instead  
19 of the onus being on the scientist to demonstrate there  
20 is a problem, has the onus now shifted to the pro-  
21 vaccine community to show that there isn't a problem?  
22 And remembering my patron sitting there in Africa, what

1 does it all mean for him or her? Well, there is  
2 balancing scales out there, and there is a theoretical  
3 risk from thimerosal that we are all aware of and have  
4 been discussing. On the other hand, there is the known  
5 risk from vaccine-preventable diseases if we stop  
6 immunization and if we're no longer able to use the  
7 vaccines that we have at the moment and which have been  
8 used successfully for fifty to sixty years. And there  
9 is the known risk from contamination of vaccines. I  
10 put it to you that it is not a nearly equal balance.  
11 It is a balance which is, without hesitation, in favor  
12 of continued use on a global scale of vaccines which  
13 now contain thimerosal. Thank you.

14 (APPLAUSE)

15 **DR. GREENBERG:** Thank you, Dr. Clements.

16 Do we have any questions?

17 **DR. GELLEN:** Bruce Gellen from the Infectious Disease  
18 Society.

19 John, has this -- the decision that's been made here  
20 and some of the recommendations, has this trickled into  
21 developing country programs and has there been some  
22 discussion to date at local levels?

1       **DR. CLEMENTS:** When the United States generated this  
2 interest and it went public on the Internet and in the  
3 journals, then WHO put out a press release and  
4 distributed information and backup information to all  
5 EPI managers throughout the world and to WHO regional  
6 offices and country representatives. And to my delight  
7 and amazement, I had only one e-mail query of  
8 clarification following that.

9       So at this point the world is quiet, and I'm very happy  
10 to say that. So it doesn't seem to have had any impact  
11 at all, Bruce.

12       **DR. HALSEY:** John, the cost of --

13       **DR. GREENBERG:** Identify yourself, Neal.

14       **DR. HALSEY:** Neal Halsey. The cost that you put in for  
15 the potential use of single-dose or mono-dose vials and  
16 so forth, because of the increase in space  
17 requirements, you estimated it would increase to five  
18 hundred million per year, but you didn't give us what  
19 the current cost is and whether that increase in cost  
20 is a single time or whether that's recurring year after  
21 year after year. I recognize that more refrigerators  
22 would need to be purchased at multiple points in the

1 cold chain, but once those are purchased, then that --  
2 is that -- I asking, is that a one-time cost and, you  
3 know, what is the recurring cost?

4 **DR. CLEMENTS:** Okay. There are two parts to that.  
5 It's approximately doubling the cost of the cold chain  
6 to half a billion, and most of that would be capital  
7 investment, not recurring costs.

8 **DR. KATZ:** Sam Katz from Duke University and the  
9 Infectious Disease Society of America.

10 John, one of the issues that we have heard repeatedly,  
11 and this may not be a fair analogy, but that is what  
12 the United States policy determines regarding vaccine  
13 use has effects on the WHO program. That came up with  
14 smallpox vaccine when we discontinued use six years  
15 before WHO. More recently, concerns switching to IPV  
16 and rejecting OPV as the vaccine of choice in this  
17 country. And one side, of course, is your pragmatic  
18 issue: Do thimerosal-containing vaccines remain  
19 available?

20 The other is, perhaps, related to what Bruce Gellen was  
21 asking, which is its influence on policymakers in other  
22 countries, particularly the developing nations. Do you

1 see this as an issue?

2 **DR. CLEMENTS:** It's potentially an issue. I think a  
3 lot of countries use whatever the FDA does as a  
4 benchmark, and in my own country, New Zealand does the  
5 same. It looks to FDA, and if it passes a vaccine,  
6 that in itself is crucial in the vaccine being accepted  
7 in that country.

8 Do they accept it without process? No. And I think  
9 our job has been in this last few weeks to be the  
10 moderator of the information coming out of the United  
11 States and to say that has been deliberated in the  
12 United States and it has relevance to that country, but  
13 it needs to be processed and seen in the light, in this  
14 particular light, for the rest of the world.

15 So, yes, it has a powerful influence, but countries  
16 make their judgments. The end call is that they make  
17 their own judgments.

18 **DR. SNIDER:** Dixie Snider, CDC.

19 John, How do you see moving forward on this from a  
20 global perspective? I mean, it seems to me, as you've  
21 indicated, it's going to be a long process, and I'm  
22 very concerned about the trends, as you pointed out,

1 were to use local producers, and there are a lot of  
2 reasons for that, which we -- you may want to elaborate  
3 on. But there seems to be, by doing that, an increased  
4 need for a preservative if you're going to rely on a  
5 variety of local producers, unless somehow GMP, Good  
6 Manufacturing Practices, can be upgraded in many of  
7 these countries.

8 And so I wonder, realistically, how do you see this  
9 playing out to achieve the goal of maintaining the  
10 availability of these necessary vaccines while at the  
11 same time getting the mercury out?

12 **DR. CLEMENTS:** I think we have perhaps a different  
13 perspective on the urgency. I think the United States  
14 is faced with a different set of pressures from some  
15 other countries and it must respond to them.

16 But I think our job in WHO is to guide in as wise a way  
17 -- I wish I could remember what Stan's quote was -- to  
18 have the wisdom to guide countries in making decisions  
19 in an appropriate time base.

20 And what we'll be doing is working with the Experts  
21 Committee on Biological Standardization to come up with  
22 something similar to the European vaccine manufacturers

1 in encouraging a gradual shift towards mercury-free  
2 preservatives, but it will be something which is  
3 measured in due time and with due consideration of as  
4 many factors as necessary.

5 So I think that's how I'd answer it. We will  
6 definitely be encouraging the process. We will  
7 probably be funding research from researchers who wish  
8 to investigate the potential for new preservatives.  
9 We'll be looking at industry and encouraging them to do  
10 the research.

11 There will be -- We'll be putting out feelers in many  
12 directions to try and encourage the development, the  
13 rapid development of that preservative, because for us  
14 there is no turning back from multi-dose vials and  
15 there is no getting away from the fact that due to  
16 human error, potential for human error, it is essential  
17 that those multi-dose vials have some preservative  
18 system in them.

19 **DR. PLOTKIN:** Plotkin, PMC.

20 I'd just like to point out that there's been kind of a  
21 subtle fall down the slippery slope here. That is to  
22 say, the discussions have started out by talking about

1 limits, tolerable limits, to the amount of mercury, and  
2 now we're talking about zero tolerance. So we've now  
3 progressed -- I'm generalizing here, of course. We've  
4 now progressed to the point where no mercury is  
5 tolerable at all, whether it meets EPA requirements or  
6 not.

7 Now, in the particular situation of the developing  
8 world, John, I mean, could you not envision a situation  
9 where there would be an allowable amount of mercury  
10 given in the multi-dose vaccines, considering that in  
11 the developing world the number of vaccines being used  
12 in not the same as in the U.S.?

13 **DR. CLEMENTS:** Well, I think, Stan, you made a  
14 rhetorical statement there which I certainly don't  
15 agree with, that we're wanting zero dose mercury. That  
16 has not been established in any scientific setting. It  
17 may be an emotional response which you're talking about  
18 on a slippery slope, but mercury ingestion and  
19 environmental mercury that we have around us now make  
20 it impossible to think that we'll be mercury-free.  
21 What we're talking about is how much mercury is  
22 acceptable. That doesn't negate the desire -- the

1 desirability of having mercury-free vaccines, but we  
2 certainly are not targeting that as -- that is not  
3 necessarily our immediate goal, although it may be our  
4 long-term desirability.

5 Thimerosal has been a fantastic preservative for fifty  
6 to sixty years, and it has done a fantastic job.

7 **DR. WANACOTT:** I'm not sure whether we have  
8 representation -- I'm Dave Wanacott from Merck. And  
9 I'm not sure if we have representation from the  
10 Pharmacopeia decisionmakers in this meeting, but have  
11 you considered at WHO talking to some of the  
12 pharmacopeias? Because they have really been a large  
13 driver for the higher levels of preservatives to meet  
14 the antimicrobial effectiveness testing, and they  
15 consider backing off on both levels. Has that  
16 consideration been discussed?

17 **DR. CLEMENTS:** Yes. I'm speaking from a particular  
18 unit in WHO, the Immunization Unit. We work hand-in-  
19 hand with Biologicals. So I'm not privy to everything  
20 to the Chief, L. Wynn Griffith, has been doing in that  
21 area, but I know he has been in contact with them, and  
22 absolutely, I think it's a good point.

1 **DR. GREENBERG:** Well, we're actually a little bit  
2 early. So I'd like to ask whether there are any  
3 questions for our last two speakers, after you've heard  
4 all three, or whether any of the speakers have anything  
5 to say to the other speakers that might be informative  
6 or help clarify this issue?

7 Bill?

8 **DR. EGAN:** If I could just make a comment. First of  
9 all, thimerosal, or if you want to go on the other side  
10 of the Atlantic, thimerosal, has not been banned. So  
11 we're not talking about that it must come out of all  
12 vaccine. So, you know, thimerosal has not been banned.

13 We are, nonetheless, concerned about the cumulative  
14 doses of mercury and we prefer to have mercury-free  
15 vaccines and preservative-free vaccines, i.e., single-  
16 dose presentations in the United States.

17 We have asked manufacturers for their -- you know, for  
18 their plans for elimination of thimerosal and that  
19 it'll still be a -- you know, if they cannot eliminate  
20 it, to justify it and be allowed where justified. So,  
21 you know, we haven't gone to that point of saying, you  
22 know, as of such and such a date, mercury cannot be in

1 any preservative -- in any vaccine.

2 **DR. SNIDER:** Dixie Snider. I just wanted to raise one  
3 additional point that I think has been implied but  
4 really hasn't been made explicit, and that is that I  
5 think the -- there is an important issue here around  
6 the credibility of immunization programs nationally and  
7 globally, and that although it may not be in the best  
8 interests of everyone to eliminate mercury entirely  
9 because the risk or the price of doing so might be a  
10 price we don't want to pay, I think the concern about  
11 the integrity of the entire immunization effort, if you  
12 will, has been on many people's minds and has been a  
13 part of the decision-making process up to this point  
14 and will continue to be a part of the consideration  
15 here. Not that people do not want to react to  
16 scientific information that is available in an  
17 appropriate way, but, in addition, when there are  
18 choices that can be made to move from a thimerosal-  
19 containing vaccine to one which is -- can be found to  
20 be just as safe and effective without that agent, then  
21 it's to the immunizations programs' advantage to be  
22 seen as not adding to the mercury that people are

1 ingesting all the time, not be adding to mercury  
2 burden.

3 So I think the credibility of all immunization programs  
4 is important to maintain, and one aspect of the reason  
5 why we have declared concern, if you will, about the  
6 amount of mercury that we are delivering.

7 **DR. ZUNE:** Kathy Zune, CBER.

8 I just wanted to make one comment regarding the issue  
9 of the timing here, and it was alluded to that this was  
10 rather sudden. The issue and concern over thimerosal  
11 has been an ongoing discussion, and I think the  
12 discussions with manufacturers looking at the reduction  
13 and/or elimination of thimerosal is not a new issue. I  
14 think some of the aspects which triggered some of the  
15 current information that has been discussed has been  
16 during the FDA Modernization Act of 1997. We were  
17 directed at the FDA to do an evaluation of mercurials  
18 in all FDA-regulated products. As part of that  
19 initiative we worked cooperatively with the  
20 manufacturers to get the data, which is what you will  
21 be hearing later in the workshop. The issues are then  
22 looking at cumulative levels, as was discussed by Dr.

1 Snider, I think became the issue of concern. The  
2 vaccines are believed, when looked at, safe and  
3 effective, but when you're looking at cumulative does  
4 in small neonate typing, I think the issue and the  
5 concern was raised and should be looked into, both from  
6 a scientific as well as a public health issue.

7 My sense is that this workshop is very valuable to the  
8 public health service, FDA included, in order to have a  
9 very important scientific evaluation of the data  
10 available and what data we need to get. So, thank you.

11 **DR. GREENBERG:** Dr. Plotkin.

12 **DR. PLOTKIN:** Well, several points. One, actually, in  
13 responding to Dr. Zune, I think  
14 the -- there is general agreement that mercury is not going  
15 to be used in future vaccines. I think the issue is  
16 more whether it needs to be removed immediately from  
17 currently licensed vaccines.

18 In relation to Dixie Snider's comment, I would like to  
19 say that if anti-vaccinationists did not have mercury,  
20 they would have another issue, and one cannot prevent  
21 them from making hay regardless of whether the sun is  
22 shining or not. So I don't think that's really a valid

1 reason for making decisions.

2 Lastly, I don't want to lose sight of the comment by, I  
3 think Dr. Wannake from Merck. I am certainly not a  
4 vaccine production person, but in looking at the  
5 Pharmacopeia regulations, I was struck by their, let's  
6 say, apparent excessiveness, and whether one could --  
7 And this is actually be considered in Europe, whether  
8 one could adopt different criteria which would allow  
9 reduction of the concentration of preservatives in  
10 vaccines. In other words, that you would require only  
11 stasis rather than cetyl activity against  $10^5$  or  $10^6$   
12 organisms, as Bill Egan mentioned.

13 **DR. GREENBERG:** I know less about this than Dr.  
14 Plotkin, but it certainly seems to me that the biologic  
15 experiment, there's a lot to be said for that, but it  
16 doesn't seem to me that usually contamination should be  
17 occurring at quite that level and that you might be  
18 able to get exactly the same effect with less than --  
19 If somebody in the audience knows how that criteria --  
20 what the thought process behind it was, that would be  
21 an interesting thing to hear about.

22 Bill?

1       **DR. EGAN:** I can't comment about, you know, the thought  
2 process, and it goes back quite a few years, I think  
3 somewhere around 1970, when the USP introduced those  
4 requirements, their definition of a preservative, but I  
5 would like to add again what I mentioned during my  
6 talk, that I did think that, you know, those are very  
7 stringent requirements and that the -- that in the  
8 United States, it is not necessary that a preservative  
9 per, you know, the CFR must meet the USP definition.  
10 Certainly, that's -- you know, that's acceptable, and  
11 it has been, but it's not a requirement that it meet  
12 the USP to satisfy the CFR. I did run that through our  
13 general counsel.

14       **DR. GREENBERG:** All the pharma -- Did the big pharma  
15 hear that last statement?

16       **UNIDENTIFIED SPEAKER:** Just one comment. Usually when  
17 we're manufacturing, we think on the international  
18 level, and, particularly, it's the European  
19 Pharmacopeia that is the mandatory one, and their  
20 requirements are perhaps even more strict than the USP.  
21 therefore, you know, I'm thinking in the international  
22 scheme of things, that becomes an issue.

1 Let me give you an example. A few years ago, quite a  
2 few years ago, we were working with the Europeans and  
3 taking a product that's no longer -- a diluent that's  
4 no longer on the market that had a preservative in it,  
5 and it was a single-dose vial, but there was a very low  
6 level of thimerosal in it which would not pass the  
7 European Pharmacopeia. And we said, well, basically  
8 this is a single dose, it's there as assurance for  
9 misuse after it leaves the manufacturer. And they  
10 said, well, no, still got to meet European  
11 Pharmacopeia.

12 so I think that needs to be brought into the equation  
13 here in looking to evaluate some of these requirements  
14 that may not be a requirement in the U.S., but our  
15 impact on the international basis.

16 **DR. SNIDER:** Dixie Snider again.

17 I just wanted to respond to Stan by saying that I  
18 wasn't speaking -- in talking about credibility, I  
19 wasn't speaking to try to address issues that anti-  
20 vaccine groups might raise because I do realize that  
21 there are incredibly an unending list of complaints or  
22 charges that could be made.

1 I'm more concerned, though, about scientists at the  
2 Agency for Toxic Substances and Disease Registry and  
3 the National Center for Environmental Health and the  
4 Environmental Protection Agency and others who have  
5 expressed concerns about the mercury that we are  
6 delivering and was only trying to suggest that, in view  
7 of concerns of scientific groups, it is reasonable to  
8 consider how we can lower or eliminate the mercury that  
9 we deliver through vaccines since people will get it  
10 through, unavoidably, a series of food supply.

11 **DR. GREENBERG:** Dr. Klein?

12 **DR. KLEIN:** Jerry Klein, the Boston University.  
13 Stan, as a point of information, could you clarify the  
14 many products that do not have thimerosal? Now, do  
15 they have other preservatives, or are they free of any  
16 preservatives? And if so, what is the basis for their  
17 success and is it just something that is necessary for  
18 the manufacturing products in selected vaccines? As  
19 example, there's one pneumococcal vaccine that has  
20 thimerosal, as the alternative product does not, and  
21 the same thing with amphophilous influenza.

22 **DR. PLOTKIN:** Well, there are many parts to that

1 question. The best table on the list of vaccines  
2 containing thimerosal is the one published by the AAP,  
3 and I refer to it often. But as Bill mentioned, IPV  
4 contains 2-phenoxyethanol because thimerosal will  
5 inactivate the polio component. Other than that, I  
6 think -- I think, but I'm not absolutely certain, that  
7 benzyl alcohol may be in some unusual vaccines, but in  
8 terms of common vaccines, I think those are the only  
9 two.

10 Now, why is TM, to give a nondenominational name -- why  
11 is it present? Usually because manufacturers are  
12 making multi-dose and single dose and prefer to have  
13 one product that they fill from.

14 Now, of course, as I stressed, where single-dose  
15 presentations are the only form, you can, in fact, do  
16 simple aseptic filling with the risks that Bill  
17 mentioned.

18 So the choice of whether there's TM in it or not  
19 depends on largely what forms are being made, whether  
20 bulks have to sit around for some time before they're  
21 combined for filling, and issues which relate to the  
22 perceived production process and the subsequent use --

1 that is, the subsequent use by physicians -- whether in  
2 the single-dose form or in the multi-dose form, and  
3 also capacity of the manufacturer to make one or the  
4 other.

5 I'm not sure that I've answered your question very  
6 precisely, but I -- that's about the closest I can  
7 come.

8 **UNIDENTIFIED SPEAKER:** But there are a number of  
9 products that appear to be in multi-dose form that do  
10 not have preservatives?

11 **DR. PLOTKIN:** No.

12 **UNIDENTIFIED SPEAKER:** So any multi-dose form does have  
13 a preservative?

14 **DR. GREENBERG:** Well, I think we're almost back exactly  
15 on schedule, which is good. You can all take a thirty-  
16 three-minute break, so 11:00 o'clock, and be back in  
17 your seats then. Thank you.

18 (RECESS FROM 10:30 A.M. TO 11:00 A.M.)

19 **DR. GREENBERG:** If everybody could take their seats,  
20 please? In the back, sit down.

21 Okay. We're now going to finish up the morning  
22 session. Before we start, I have one question that was

1 -- several people have asked, and I just wondered  
2 whether any of the speakers from the morning could  
3 answer it, and that was: For multi-dose vials --  
4 Measles/Mumps/Rubella is a multi-dose vial and does not  
5 have preservative in it -- do people know how the  
6 problems of preservation are dealt with in that  
7 vaccine? That's the question. Does anyone have an  
8 answer? A quick answer?

9 **UNIDENTIFIED SPEAKER:** (Unable to hear speaker)

10 **DR. GREENBERG:** There are no multi-dose vials of  
11 Measles/Mumps/Rubella? Somebody over there. Neal?

12 **DR. HALSEY:** My mic won't come on.

13 **DR. GREENBERG:** Okay. Then, Stan?

14 (LAUGHTER)

15 **DR. GREENBERG:** I'm not responsible. Okay. We're  
16 having -- If there's somebody in the back, the lights  
17 don't seem to be coming on. I'm going to save that for  
18 the end of the session, and people can think about  
19 that.

20 So the next speaker is Dr. Jeffery Englhardt, Senior  
21 Research Scientist at Eli Lilly, who are the -- which  
22 is the company that makes thimerosal, and his talk will

1 be "Toxicology and Metabolism of Thimerosal in  
2 Animals."

3 **DR. ENGLHARDT:** Thank you. I appreciate Dr. Myers'  
4 invitation to come to this. I am a veterinary  
5 pathologist, so I look at things from a slightly  
6 different perspective in that I work in the toxicology  
7 or drug safety component of Eli Lilly and Company.  
8 When the question came to me about toxicity of  
9 thimerosal, I had to scratch my head and wonder, what  
10 the heck is this? This is not a product that I have on  
11 my horizon very often, and I had to talk to one of my  
12 more senior colleagues who said, "Oh, that's  
13 Merthiolate." As I started getting into this  
14 particular topic, I had to go back into our corporate  
15 literature but also start searching the scientific  
16 literature. Though we keep information from a material  
17 safety data sheet standpoint, we don't keep an active  
18 research program going on this compound, mostly because  
19 of its historical perspective. If you'll bear with me  
20 a little bit, I'd like to take a few minutes to retread  
21 some of the ground that was covered this morning, but  
22 it's important to, I think, see where the database has

1 grown on the toxicity of this compound and where are  
2 the holes in terms of the toxicity of this compound.  
3 As was mentioned earlier, thimerosal is an  
4 organomercurial. It's ethylmercurithiosalicylate and  
5 it's just mercury that's part of the ethylmercury that  
6 has apparently become the issue that's being discussed  
7 here at this workshop. And just to note from a  
8 molecular standpoint, in this complex salt, the mercury  
9 composes about forty-nine percent of the molecule.

10 Looking back into the historical literature, thimerosal  
11 had a variety of chemical properties that made it very  
12 attractive. And one of the things also, as I was  
13 reading this literature, is that not all mercuries are  
14 alike, and I'd like to retread that again a little bit  
15 later in the talk. Now, thimerosal is found to be very  
16 water soluble. It was created stable solutions and  
17 also compatible with a variety of biological materials.

18 As Dr. Klein mentioned earlier, we were one of the  
19 first to be using thimerosal as a preservative in some  
20 of our older vaccine days in terms of the diphtheria  
21 vaccine. It was also used in some of our other toxoids  
22 that were produced back in the '30s and '40s. And as

1 mentioned also, this has been marketed since the '30s,  
2 and as I got into our literature, I found that there is  
3 very little in terms of toxicology in animals. Most of  
4 it is quite old -- The primary reference is a 1931  
5 reference in the American Journal of Hygiene -- and  
6 it's often in obscure journals or cited as one or two  
7 sentences within review articles, and it's very  
8 difficult to find very explicit information on  
9 thimerosal.

10 As has been well described this morning, it's been used  
11 as an antiseptic, fungistat, and a preservative for a  
12 number of years. The antimicrobial activity has been  
13 attributed to the release of this ethyl mercuric ion  
14 and thereby acting as an oxidizer for groups leading to  
15 changes in intracellular calcium and that is the  
16 mechanism that it causes cell death. I also found that  
17 it's very interesting that there are as many articles  
18 on using thimerosal as an in vitro reagent to study the  
19 calcium fluxes in cells as there are uses for -- or  
20 publications on use in vaccines.

21 One thing that I did find is that the ethylmercury and  
22 thiosalicylate are the primary metabolites which were

1 described in an article published from Lilly in 1956.  
2 In this particular issue, they were looking at the  
3 question around the inactivation of IPV with the use of  
4 thimerosal and had discovered that these metabolite  
5 ratios can be altered by the presence of copper within  
6 either the vials that are being filled or within the  
7 production materials and that the copper drives the  
8 reaction not to the mercuric ion, but to the mercuric  
9 oxide. That is one of the materials that is purported  
10 to inactivate the protein in the polio toxoid.

11 So, so much for the history. What I'd like to do now  
12 is talk a little bit about what do we know about the  
13 toxicity of this molecule. Again, these data are from  
14 some of these older articles. There's been nothing  
15 that I've been able to uncover published in about the  
16 past twenty-five years in terms of new animal data on  
17 this molecule.

18 Oral toxicity in rats has a MLD of about 73 mg/kg and,  
19 as you can see, when you look at the rodents and the  
20 lagamorphs (sic), there is a disparity in terms of  
21 what the bodyweight toxicity is, but the overriding  
22 morphological alteration that occurs in these animals

1 is renal necrosis. This is interesting in the fact  
2 that this type of toxicity is what has been described  
3 most widely with mercuric chloride studies, which is  
4 renal necrosis.

5 One human study -- And I should note that I found a  
6 couple of human correlates to go along with this during  
7 my searches. There was one human accidental or -- I  
8 can't say if it was accidental. It must have been  
9 intentional in this case. An individual consumed some  
10 liquid Merthiolate and successfully done himself in.  
11 He consumed an estimated 83 mg/kg showing that the oral  
12 toxicity in rats is pretty well on, but the  
13 presentation that this individual had was, again, very  
14 similar to what's been seen with mercuric chloride,  
15 that he presented with gastritis, renal failure, and  
16 gingivitis. It wasn't until the very late stages  
17 before he died of respiratory failure that any type of  
18 polyneuropathy was identified.

19 Also as mentioned earlier, thimerosal is a very  
20 exquisite antigen, not only in people but also in  
21 guinea pigs and rabbits, and it is also a dermal  
22 irritant as was described in some of the earlier

1 literature when thimerosal was used as a contact lens  
2 solution preservative. The ethylmercuric chloride is  
3 the purported allergen that's responsible for these  
4 phenomena not only in people but also in animals, and  
5 one of the disparities from the animal studies that's  
6 been identified is that, unlike people that can  
7 occasionally have a systemic hypersensitivity reaction,  
8 those particular phenomena have not been identified in  
9 either the rabbit or the guinea pig studies.

10 When we start looking at the non-rodent species, the  
11 only studies that I had found on toxicity were some in  
12 the 1931 publication on toxicity in dogs, where 2 mg/kg  
13 was administered every three days and then 10 mg once  
14 weekly over a six-week period, and at the end of that  
15 the animals were examined and there were no -- there  
16 was no clinical toxicity nor pathologic alterations  
17 that were identified.

18 I was also surprised to find that there was a two-year  
19 carcinogenicity study that had been conducted on  
20 vaccine preservatives and thimerosal was included in  
21 that particular study, and the outcome of that was that  
22 there were no compound-induced neoplasms. It should

1 also be noted that thimerosal does cross the  
2 blood/brain barrier. It also crosses the placental  
3 barrier. However, there has not been any evidence of  
4 turadnogenicity (phonetic) that's been shown with the  
5 compound in a study that was conducted with one of the  
6 contact lens preservatives.

7 It should also be noted -- And this is one of the gaps  
8 that I identified and this is part of the concerns that  
9 are raised here in looking at the neonatal vaccine  
10 issue -- is that typically now with the pharmaceutical  
11 agents, we do what's called a post-natal development  
12 study or a Segment III study, and there's nothing in  
13 the literature right now that has anything that looks  
14 at in utero exposure to thimerosal and in post-natal  
15 development in rodents. So we do not have any data  
16 that would indicate either a risk or a lack thereof.  
17 I did find one article that I found very informative  
18 and that was an article published in 1975 by Blair, et  
19 al., that was looking at the metabolism and excretion  
20 of thimerosal in adult squirrel monkeys and this was a  
21 chronic study, a chronic daily administration study.  
22 Thimerosal, at a concentration of .002 percent, and

1 this is, I believe, in the range of what's used as a  
2 preservative in the vaccines. I think that's allowed  
3 to go up to about .01 percent. This was administered  
4 in two ranges, either 2.2 or 12 micrograms per monkey  
5 per day for six months and that the total thimerosal  
6 dose was 418 or 2280 micrograms. If you remember, this  
7 has a 49 percent of mercury, so this means that these  
8 animals received roughly 200 micrograms of mercury or  
9 1100 micrograms of mercury.

10 Now, this is a classic tissue distribution study and,  
11 unlike what's done with pharmaceutical agents, they had  
12 to use atomic absorption to look for the mercury. So  
13 the tissues were dissected, analyzed for the presence  
14 of mercury and what form was that mercury in and also  
15 histologic evaluation of those tissues to see if there  
16 were any accompanying morphologic alterations due to  
17 the presence of absence of the mercury.

18 The data from this study showed that there was no  
19 evidence of toxicity either seen clinically during that  
20 six-month administration phase or during the pathology  
21 evaluations. There was variation in the mercury  
22 concentration in individuals. That is, within those

1 given groups, there was a disparity in how much  
2 mercury, even though they were given the same dose by  
3 the same period of time, on how much mercury was  
4 accumulated in different tissues, but what was of note  
5 was that the mercury that was present in the blood and  
6 tissues was primarily in the inorganic form and also  
7 that the distribution of the  
8 tissues -- or within the tissues had kidney as being the  
9 primary organ, followed by liver, muscle, brain, and  
10 the least of all, in blood.

11 Now, some of this conversion from the organic to the  
12 inorganic may lead to the point that I made earlier,  
13 that all mercuries are not alike and that within the  
14 organomercurials, there is a difference in the  
15 stability of that carbon/mercury bond, and I'm hoping  
16 that when Mr. Lucier presents later, talking about  
17 ethyl and methylmercury that he will be striking on  
18 that.

19 It also should be noted that the ethylmercury  
20 compounds, particularly thimerosal, will also undergo  
21 this biotransformation of organic to inorganic in human  
22 tissues, and that was described in a report by Suzuki

1 in 1971.

2 As I mentioned, the kidney had the highest  
3 concentration, and you can see we've got over 3000  
4 nanograms -- These are the mean values that were  
5 presented in this article -- and that the predominant  
6 form that was present within the kidney tissue was  
7 inorganic. And as you go through, you can see that  
8 from the kidney, as you move down, there is a quite a  
9 disparity between the average values that were present  
10 in the brain in terms of inorganic mercury and what was  
11 present in the major excretory organ and very little  
12 present in the blood.

13 Again, there was no evidence of toxicity seen  
14 clinically or evidenced morphologically that the  
15 presence of this mercury was causing any deleterious  
16 effect on these animals.

17 One thing that was brought out in this article is they  
18 mentioned that a critical brain level of mercury range  
19 from 3 to 9 micrograms per gram in the brain to cause  
20 toxic effects. What should be noted is that even  
21 though there were differences among all these animals,  
22 the highest level in the high-dose animals was only 245

1 nanograms per gram in the brain and 73 percent of that  
2 was organic. Now, what this article did not provide us  
3 was elimination data. We do not know how rapidly the  
4 mercury that was within the animals was removed.  
5 However, one could extrapolate that since this is  
6 present primarily in an inorganic form that it would  
7 likely follow the types of kinetics that have been  
8 described experimentally for inorganic mercury. There  
9 was an abstract presented at the 1998 Society of  
10 Toxicology meeting looking at a population  
11 pharmacokinetic study following mercury vapor exposure  
12 in humans that determined that the half-life in the  
13 kidney compartment was roughly nine days. So if you  
14 start thinking of the amount that is given as part of a  
15 preservative relative to the accumulation that was seen  
16 over six months daily administration in this study,  
17 there may be some disparities in terms of toxicity  
18 relevance from what we know in the animal studies.  
19 And one of the differences between methyl and  
20 ethylmercury, if this is -- and also the inorganic  
21 mercury is that if this is present inorganic form, it  
22 should be eliminated more rapidly than what's known for

1 methylmercury. It's known that the inorganic forms are  
2 removed more rapidly than methyl. Also with inorganic,  
3 about 50 percent of the material is eliminated in the  
4 feces without enterohepatic circulation which known for  
5 the methyl form.

6 In summary, I'd just like to say that the animal  
7 studies that have been conducted, even though they are  
8 very limited, have looked at doses that are greater to  
9 or equal than what's present in preservatives. What we  
10 did find in terms of the acute lethal dose is that  
11 there seems to be some correlation between the one  
12 human study -- or one human case report that I  
13 uncovered and what the animal studies indicate and that  
14 the presentation does look very much like what's been  
15 described in the literature for the mercuric chloride  
16 studies and that renal toxicity is the primary  
17 alteration and this occurred only at high doses in all  
18 of these animal studies.

19 This particular change may also be consistent with the  
20 kidney being the primary organ of accumulation that was  
21 seen in this study by Blair. It should also be noted  
22 that at no time in any of these animal studies that

1 have been described was there any evidence of  
2 neurotoxicity or morphologic alterations anywhere  
3 within the brain.

4 This is a very exquisite dermal irritant and allergen  
5 and as I went through the literature, I found a  
6 plethora of reports on allergic reactions and this is a  
7 very important issue in its own right, not to downplay  
8 anything relative to the accumulation of mercury, but  
9 the mercury itself is present within blood and tissues  
10 and generally within the -- as an inorganic. From that  
11 standpoint, its particular relevance in terms of  
12 cumulative effects and, again, its tissue distribution,  
13 I hope are considered as part of the toxicity  
14 information when you're deliberating how to look at  
15 alternatives and really what the toxicity issues are  
16 with thimerosal.

17 So that's the end of what I have. Again, it's over  
18 old, very limited, and in difficult-to-find places, and  
19 I thank of our archivists for having some of these  
20 older articles around. If it weren't for them, I  
21 probably would not have uncovered some of this  
22 information.



1 neurodevelopmental aspects?

2 **DR. ENGLHARDT:** That's correct. That's one of the gaps  
3 that I identified, the lack of the postnatal  
4 development study. That's typically where we would  
5 pick these things up. You expose the fetus as you  
6 would in the teratology study but allow the delivery to  
7 take place and then do the behavioral assessments  
8 postnatally. And no data relative to that was present  
9 in any of the literature packs. Again, that would get  
10 after your question.

11 **UNIDENTIFIED SPEAKER:** (inaudible) and Disease  
12 Registry.

13 Is there any data to show how rapidly the ethylmercury  
14 that's broken through (inaudible) the thimerosal?

15 **DR. ENGLHARDT:** I did not see any kinetic data other  
16 than this biotransformation will occur, not only in  
17 circulation but also in tissues. The report by Suzuki  
18 was cited in an article by Dr. Clarkson and the  
19 original article was in Japanese and I was unable to  
20 understand that, but I believe that kinetics were  
21 discussed because there were x/vebo (phonetic) studies  
22 that were also cited. Unfortunately, I can't give you

1 a kinetic number for that. All we know is that there  
2 is conversion, but how rapidly that occurs, we don't  
3 know.

4 **DR. KILBOURNE:** The acute toxicity studies that you  
5 showed -- I'm sorry. My name is Ed Kilbourne from NC -  
6 - from CDC, NCEH.

7 The acute toxicity studies that you showed, were those  
8 LD 50's?

9 **DR. ENGLHARDT:** Yeah, those are LD 50 or MLD's.

10 **DR. KILBOURNE:** And I'm sorry, but I didn't get the  
11 units of the organ-specific concentrations that you  
12 showed later on.

13 **DR. ENGLHARDT:** Those are nanogram per gram.

14 **DR. KILBOURNE:** Okay. Thank you.

15 **DR. ENGLHARDT:** So even much less than what was  
16 presented earlier from the Faroe Islands study because  
17 those were all microgram per gram concentrations.

18 **UNIDENTIFIED SPEAKER:** (Inaudible) Is there any  
19 evidence or is there anything known whether the  
20 compound, the ethylmercury, is covalently bound to  
21 proteins?

22 **DR. ENGLHARDT:** There is nothing on covalent binding to

1 proteins. We do know that the mercuric ion will react  
2 with subhydrol groups. So if you figure the number of  
3 sistines that may be present in any given protein, you  
4 can have oxidation of that subhydral reading to a  
5 denaturative event, but there's nothing that says that  
6 there is covalent binding to that particular protein.  
7 Even some of the in vitro studies haven't addressed  
8 that question.

9 **DR. GREENBERG:** Anymore questions?

10 (NO RESPONSE WAS HEARD)

11 **DR. GREENBERG:** The last speaker of the morning is Dr.  
12 Leslie Ball, who is the Medical Officer at the Center  
13 for Biologics Evaluation, FDA, and she is going to talk  
14 on "Thimerosal in Vaccines."

15 **DR. BALL:** I would like to thank Dr. Myers and the  
16 other organizers for the opportunity to discuss the  
17 findings of our review on the use of thimerosal in  
18 vaccines.

19 Specifically, what I will be reviewing today is the FDA  
20 safety assessment of thimerosal in vaccines. We  
21 concentrated our review on vaccines that are used in  
22 infants because this is population that is receiving

1 the largest dose of thimerosal per kilogram and,  
2 because the developing brain of infants, may be  
3 affected by a mercury-containing compound, including  
4 preservatives.

5 I think much of this has already been covered. We all  
6 know that thimerosal is the most widely used  
7 preservative in vaccines. It's present in over 30  
8 licensed U.S. vaccines, in concentrations of .003  
9 percent to .01 percent. And in the recently  
10 collated call-for-data from manufacturers, the  
11 manufacturers reported a total of 32 licensed vaccines  
12 that contained thimerosal. It's important to note that  
13 list contains products that are currently licensed and  
14 in production and distribution. And we know that there  
15 are a great deal more vaccines that are no longer in  
16 production and distribution but have been licensed with  
17 thimerosal.

18 As Dr. Zune mentioned earlier this morning, the FDA has  
19 been examining the uses of mercury-containing  
20 compounds, specifically intentionally introduced  
21 mercury into food and drugs, as a result of the FDA  
22 Modernization Act of 1997.

1 This act had three components. The first was to  
2 provide Congress with a list and analysis of the food  
3 and drugs containing mercury. This is the only  
4 component of the FDAMA that had a statutory deadline.  
5 The statutory deadline was two years from the date of  
6 enactment, or November 18th, 1999.

7 Under this provision, the FDA issued two call-for-data  
8 in the Federal Register that was directed at vaccine  
9 manufacturers, and this was a voluntary call for  
10 information. The first one was published in December  
11 of 1998 and the second was published in April of 1999.

12 The latter had a due date of June 1st, 1999.

13 The other two components consisted of the effect of  
14 mercury in nasal sprays and, finally, for the FDA to  
15 study or contract with the Institute of Medicine to  
16 study the health effects of mercury in food and drugs,  
17 specifically the adverse effects on the health of  
18 children or other sensitive populations. And it was  
19 with this latter caveat in mind that we undertook our  
20 review.

21 In terms of the relevance of this, well, you know, it's  
22 been mentioned that there's been an increase in the

1 number of vaccines recommended for routine use in  
2 infants, and there's a potential increase for exposure  
3 of infants to mercury in the form of ethylmercury from  
4 thimerosal.

5 One thing I want to emphasize, you know, I think we've  
6 all heard about the lack of data both in humans and in  
7 animals regarding thimerosal. But one thing that we  
8 kept in mind is that the absence of data of a harmful  
9 effect for a low-level exposure of infants to  
10 ethylmercury is not the same as data demonstrating the  
11 safety of thimerosal, particularly the type of effect  
12 that we're likely to observe. It's not likely to be  
13 clinical toxicity, it may not even be pathological  
14 toxicity, but it may be cognitive effects that we are  
15 concerned with, such as observed with methylmercury.  
16 I put this slide up to remind us that life was simpler  
17 not too long ago. This schedule was taken from the  
18 1988 Red Book -- This was when I was a pediatric  
19 resident -- and it demonstrated that during the first  
20 six months of life, infants only received five vaccines  
21 and only three of which, the DTP, contained thimerosal.  
22 The HIB vaccine here at this time was recommended at

1 the eighteen-month visit.

2 This slide was adapted from the 1999 ACIP, AAP, and  
3 AAFP Routine Childhood Immunization Schedule. As you  
4 can see, we have several new vaccines in the infants'  
5 schedule, including hepatitis B and HIB vaccine during  
6 the first six months of life.

7 Also note the bars here for some of the vaccines that  
8 denote the inherent flexibility in when a vaccine can  
9 be administered according to the schedule.

10 Depending on the particular brand of vaccine, as well  
11 as the schedule that is used, an infant may receive as  
12 many as nine vaccines during the first six months of  
13 life that contain thimerosal.

14 I think these -- thimerosal human toxicity has been  
15 reviewed in performing our safety assessment review the  
16 published literature on the toxicity of thimerosal, and  
17 as I stated, there have been three toxicities  
18 identified. Sensitization reaction, specifically  
19 delayed type hypersensitivity reactions were described  
20 in multiple reports after doses that are found in  
21 vaccines. It's important to note that the latter two,  
22 neurotoxicity and nephrotoxicity have only been

1 observed in very high doses and also with regard to  
2 inadvertent overexposure of thimerosal.

3 I've put together a summary list of the reports that we  
4 had, references for acute toxicity other than a  
5 sensitization reactions. The first report that I could  
6 find, well, was really just a summary report, 1941,  
7 where it looked at the therapy of bacterial  
8 endocarditis, and it reported four cases, one of which  
9 had mercury poisoning on autopsy. It was not otherwise  
10 specified how that was determined, or where, and which  
11 organs were determined.

12 Secondly, there's a report by Axton in 1972 with  
13 chloramphenicol that inadvertently had 1,000 times the  
14 dose of thimerosal added as a preservative.

15 The next case was 1977, where Fagan reported treatment  
16 of omphaloceles in neonates that received this. This  
17 is an abdominal wall defect, and they had this  
18 thimerosal coated on, and the 13 infants -- this was  
19 prompted on the basis of a sudden death of one of the  
20 infants, and they went back and reviewed the cases.  
21 This is a hospital for sick children in Toronto. And  
22 that out of the

1 ten of those died, nine of them had autopsy results, and  
2 there were mercury levels in the blood, liver, brain,  
3 and kidneys that were -- that were established in those  
4 cases. However, I would also note that similar to as  
5 has been described with the previous animal data, is  
6 that pathological changes were not demonstrated.

7 With regard to Matheson, in 1980, reported a case of --  
8 and this may be what Dr. Engler was referring to, of  
9 gamma globulin, accumulative dose. Rohyans in 1984  
10 reported the use of thimerosal irrigation of the  
11 external ear with tympanotomy tubes.

12 And Lowell, in 1996, reported the use of intravenous  
13 HBIG, off label, after a liver transplant, and the  
14 final citation was the report that was previously  
15 mentioned in the Pfab, 1996, of the thimerosal suicide  
16 attempt, 83 mg/kg was ingested. This patient did  
17 survive, but the patient did have C and S -- some C and  
18 S effects that was observed at time that he was  
19 maximally ill, as well as developing polyneuropathy and  
20 respiratory failure.

21 And to summarize these studies, some of the effects  
22 that were seen were local necrosis, acute hemolysis,

1 disseminated intravascular coagulation, acute renal  
2 tubular necrosis, obtundation, coma, and death.

3 It's also important to note that we found no evidence  
4 of data on thimerosal toxicities at the doses found in  
5 vaccines in the published literature. We queried the  
6 VAERS database for reports of adverse events attributed  
7 to thimerosal. We found 45 reports from the more than  
8 90,000 total reports that were submitted between 1990  
9 and 1998.

10 It's important to remember that here  
11 that's -- you see that most of the reports involve local  
12 hypersensitivity reactions. The most common vaccine  
13 that was identified was hepatitis B. And it's  
14 important to realize the limitations of this data.  
15 Causality cannot be inferred both because of the  
16 passive nature of VAERS and the many antigens present  
17 in vaccines in addition to thimerosal.

18 Because of this lack of data on low-dose thimerosal  
19 toxicity, we made the conservative assumption, and  
20 perhaps controversial assumption as we'll hear and  
21 we've heard already, that ethylmercury toxicity was  
22 analogous to methylmercury toxicity. Since thimerosal

1 is metabolized to ethylmercury, we looked for the --  
2 for evidence of chronic effects of methylmercury to  
3 identify risks from chronic low exposure to thimerosal.

4 Obviously, this assumption will be the point of the  
5 next session and the discussion in much of this  
6 workshop.

7 Based on two types of exposure, the first was poisoning  
8 in the Minamata Bay in Japan and, secondly, Iraq  
9 pesticide contamination with methylmercury. And the  
10 second came from population-based studies, looking at  
11 populations eating ethylmercury-contaminated fish in  
12 the daily diet, such as the Seychelle and the Faroe  
13 Islands. We concluded that one of the possible risks  
14 of low-dose thimerosal exposure may be developmental  
15 delay.

16 On the basis of these -- the studies that I mentioned  
17 with regard to methylmercury, several organizations  
18 have set safe limits for exposure from methylmercury,  
19 primarily from the diet, and these have all been  
20 alluded to. EPA has set a limit of 0.1 microgram per  
21 kilogram per day; ATSDR has set at .3 micrograms per  
22 kilogram per day, with the FDA at .4 micrograms per

1 kilogram per day.

2 And I think one thing that I noted when we -- we noted  
3 when we did the review was that the EPA report -- sent  
4 a report to Congress that was submitted in December of  
5 1997, only made a very tangential reference to mercury  
6 in vaccines, and the mercury toxicological profile that  
7 was published by the ATSDR also did not look  
8 extensively at the issue of ethylmercury from  
9 thimerosal and vaccines.

10 And I think we'll hear in great detail the caveats that  
11 must be mentioned when using this kind of analogy.

12 First, as we mentioned, the assumption was that the  
13 methylmercury toxicity is the same as ethylmercury, and  
14 this will be discussed and debated.

15 Secondly, we did not take into consideration  
16 differences in pharmacokinetics, such as the route of  
17 administration. Methylmercury is ingested orally on a  
18 usually low-level basis, whereas the route of  
19 administration for thimerosal is intramuscular, kind of  
20 in a bolus-type exposure.

21 Also, there is, as I mentioned, differences in daily  
22 schedule and the magnitude of doses and the possible

1 differences in elimination, and we've already heard  
2 about some of those differences.

3 So next what we looked at was what the exposure of  
4 infants to methylmercury is from the U.S. Recommended  
5 Vaccination Schedule and how it compares to suggested  
6 limits for safe intake of methylmercury.

7 As I mentioned, this is the final concentration of  
8 thimerosal in vaccines. It is -- If it's present in  
9 multi-dose vials, it's often but not always present in  
10 single-dose vials. One example of this is HIB vaccine.

11 And as we have heard, thimerosal is 49.5 mercury by  
12 weight in the form of ethylmercury. An example of the  
13 calculation of the amount of thimerosal -- I'm sorry,  
14 the amount of mercury can be done this way. Hepatitis  
15 B vaccine is .005 percent thimerosal and is added in  
16 the final concentration. It's 15 micrograms of  
17 thimerosal per 1 ml, or 25 micrograms of thimerosal per  
18 half and ml, which would translate into 12.5 micrograms  
19 of mercury for a half-a-ml dose.

20 These are the U.S. licensed vaccines containing  
21 thimerosal. We've all seen this in the AAP interim  
22 report. There is additional vaccines that are -- that

1 contain thimerosal, I think as was pointed out.  
2 Influenza, all of the vaccines contain thimerosal. In  
3 addition, there is one pneumococcal vaccine that  
4 contains thimerosal and one that does not.  
5 This list is a list of thimerosal-free U.S. licensed  
6 vaccines that are given routinely in infants and  
7 children. This is not an exhaustive list. Obviously,  
8 there are more vaccines that do not contain thimerosal.

9 But you can see DTaP, there is one. HIB, several  
10 preparations. There's a combination HIB/hepatitis B.  
11 Then there are these additional vaccines. There are no  
12 U.S. licensed thimerosal-free products for these  
13 vaccines.

14 So next what we did was, we calculated the maximum of  
15 exposure of thimerosal from vaccines and infants less  
16 than or equal to six months of age. And at six months,  
17 according to the recommended schedule, an infant may  
18 receive three DTaP vaccines, three HIB vaccines, three  
19 hepatitis B if it's given on the schedule in which the  
20 last dose is at six months, and in selected  
21 populations, influenza vaccine may be given. I didn't  
22 include this in the final calculation except in the

1 bracketed form. But as you can see, the total amount -  
2 - the total maximum exposure from the U.S. schedule  
3 would be 187.5 micrograms.

4 My apology to Dr. Bernier in advance for this slide. I  
5 think that this can be misinterpreted and  
6 overinterpreted, but I just wanted to say that the  
7 reason why we preformed this exercise is because of the  
8 lack of data that we had. And what we did here is, we  
9 used the suggested limits for safe intake for  
10 methylmercury from the EPA, ATSDR, and FDA that was  
11 previously shown, and it calculated the amount of  
12 methylmercury for safe intake during the first six  
13 months, or first 26 weeks, to look at what the maximal  
14 exposure would be in that six weeks -- six months.  
15 And we calculated this for the 5th, 50th, and 95th  
16 percentile for female infants, which provides the most  
17 conservative estimated limit of intake. As described  
18 by these box figures, only EPA guidelines were exceeded  
19 using the assumptions listed here.

20 Since these calculations are hypothetical, we looked to  
21 find data that mercury levels can be increased at  
22 vaccination. This study was found in an abstract in

1 "Clinical Toxicology" last year. A manuscript based on  
2 these data has recently been accepted for publication  
3 by General Pediatrics. This was done at Emory, and I  
4 think Dr. Plotkin had already mentioned this, but they  
5 looked at 15 pre-term infants. Mean weight was at 748  
6 grams for those infants and five term infants with a  
7 mean weight of 3.5 kilograms. These infants received  
8 hepatitis B within the first 48 hours of life, as was  
9 the practice for all pre-term infants in that hospital  
10 even though that did not agree with the AAP  
11 recommendations.

12 Of note here, as was previously noted, was an increase  
13 in mercury levels seen post-vaccination when compared  
14 with pre-vaccination, and this change was more  
15 noticeable in the pre-term infants. And I think that  
16 there can be problems with the methodology of this  
17 study, but I think the change here is what is salient.  
18 And we put up this slide to show that there is a  
19 minimum exposure of mercury from vaccines given to  
20 infants in the U.S. schedule. For instance, less than  
21 six months, you can -- there can be a total of zero  
22 given if you utilize this certain schedule with certain

1 products.

2 Of course, infants with hepatitis B surface-antigen-  
3 positive mothers or mothers of unknown status would  
4 still receive hepatitis B at birth.

5 In conclusion, we found that published reports of  
6 thimerosal toxicity in the form of local  
7 hypersensitivity reaction at the doses found in  
8 vaccines, that there was evidence of acute  
9 nephrotoxicity and neurotoxicity at very high doses.  
10 Thimerosal as a preservative in vaccines given in the  
11 first six months of life may result in the intake of  
12 ethylmercury that exceeds the EPA safe limits of intake  
13 for methylmercury, recognizing all the caveats that we  
14 -- that were previously stated. And, finally, infant  
15 exposure to mercury from vaccines may be avoidable by  
16 the use of thimerosal-free products.

17 And I wanted to acknowledge the contributions of Dr.  
18 Bolger from Center for Food Safety, Dr. Baylor, and Dr.  
19 Goldenthal, as well as the other participants in this  
20 review, Dr. Ball and Dr. Pratt.

21 (APPLAUSE)

22 **DR. GREENBERG:** Thank you, Dr. Ball.

1 We have some time for some questions. Dr. Plotkin?

2 **DR. PLOTKIN:** Yeah. I have a question concerning the  
3 calculation, just so that I can understand it.

4 If, let's say, for the 50th percentile, the EPA, you  
5 came up with a figure of 95 micrograms. That's based  
6 on exposure -- I assume that's based on 0.1 micrograms  
7 per kilogram per day. Is that correct?

8 **DR. BALL:** I'm sorry. Are you talking about the number  
9 that we had on the charts?

10 **DR. PLOTKIN:** Yes.

11 **DR. BALL:** That is based on the -- For each of them we  
12 did -- for EPA, ATSDR, and --

13 **DR. PLOTKIN:** Yes. And so in the EPA case, it would be  
14 0.1 microgram per kilogram per day?

15 **DR. BALL:** Uh-huh (affirmative).

16 **DR. PLOTKIN:** And that's based on how many days?

17 **DR. BALL:** It's 26 weeks of life, six months.

18 **DR. PLOTKIN:** Six months. And the number of vaccines,  
19 then, up to the six-month visit were calculated?

20 **DR. BALL:** Right.

21 **DR. PLOTKIN:** Is that right?

22 **DR. BALL:** Right. And that is assuming that on -- that

1 at the six-month visit, you know, with the maximum  
2 exposure, that they would have received all of the  
3 thimerosal-containing vaccines at that visit.

4 **DR. PLOTKIN:** My question basically is: Would it be,  
5 in your view, more or less logical to use seven months  
6 as the figure, considering that the six-month dose has  
7 to be observed, et cetera?

8 **DR. BALL:** That's a good point. I think there -- that  
9 Dr. Bernier and I have had this discussion, and, you  
10 know, I think that getting into -- without getting into  
11 the details, seventh-month may be very appropriate, but  
12 we were using a maximal exposure, given the fact that  
13 infants may receive those vaccines at the six-month  
14 visit. I think the main point is that -- And I don't  
15 have the slide there -- is that for both Dr. Bernier's  
16 calculations, as well as mine, only the EPA guideline  
17 was exceeded, not the others.

18 **DR. GREENBERG:** Can I ask for just a clarification for  
19 me?

20 Presumably what, Stan, you were getting at is that  
21 there's a blip of exceeding at six months, but if you  
22 sort of -- if you charted month 1, 2, 3, 4, 5, 6, 7, 8,

1 9, you would only see exceeding the EPA guideline at  
2 the six-month calculation, the seventh-month would then  
3 be below again, or do we know that?

4 **DR. PLOTKIN:** It was just the -- Since it's a  
5 multiplication of micrograms per kilogram per day, if  
6 you use seven months --

7 **DR. GREENBERG:** You have more days.

8 **DR. PLOTKIN:** Right, there are more days.

9 **DR. GREENBERG:** Well, then if you use eight months, you  
10 have more days --

11 **DR. PLOTKIN:** Agreed, agreed.

12 **DR. GREENBERG:** So what I'm asking is, has somebody  
13 calculated this with a graph with each -- you know, for  
14 each day for a year, and say on how many days of a year  
15 you're in excess of EPA guidelines?

16 **DR. BALL:** There has been that calculation, and if I  
17 can get it, I'll pull it up, but -- I don't want to --  
18 You know, I hesitate showing -- Dr. Barry Rumak  
19 (phonetic) did a pharmacokinetic-kind of evaluation.  
20 However, you know, I -- I'm not -- he's not here to  
21 explain the calculations that were done, but I don't  
22 know if this can be projected. Is there a possibility

1 for projecting this?

2 **DR. GREENBERG:** Is there somebody back there? Yeah.  
3 Thank you.

4 **DR. BALL:** I don't know if -- This is, you know, a  
5 representation of the hypothetical cumulative mercury  
6 body burden from vaccines in the first six months of  
7 life and looking at the kinetics of it. And, again,  
8 this is hypothetical because there aren't good data on  
9 elimination, but this is the EPA standard and this is  
10 the ATSDR standard . . . if that helps you. I'm sorry,  
11 I'm sorry. I reversed that. EPA, ATSDR. If that  
12 helps graphically . . .

13 **DR. CLARK:** Mr. Chairman?

14 **DR. GREENBERG:** Can we have the lights back on? Thank  
15 you.

16 **DR. CLARKSON:** I'm Tom Clarkson from Rochester. I  
17 talked with Dr. Barrett about these -- his  
18 calculations. Do you mind if I just show a  
19 transparency? I've done some similar calculations on  
20 this topic. Do you have time?

21 **DR. GREENBERG:** Sure, if you can move quickly.

22 (LAUGHTER)

1 **DR. CLARKSON:** This is very similar to what's been  
2 talked about as to how frequently these infants get the  
3 thimerosal. The assumption is, from my colleague from  
4 FDA, that there's a vaccine at birth where they get  
5 about 12.5 micrograms. There's a vaccine at two months  
6 where they get 62.5, one at four months where they get  
7 about 50, and one about six months where they get about  
8 62. I'm indebted to Dr. Halsey, I think, for some of  
9 these numbers here.

10 A calculation based on distribution in the body, with  
11 about 5 percent of the dose -- This is using  
12 methylmercury statistics, not ethylmercury -- with  
13 about 5 percent of the dose going to the body burden  
14 and about -- the blood volume, which Dr. Halsey gave  
15 me, of 8.5 percent bodyweight, you get blood numbers  
16 like this, that there is this sawtooth effect of a  
17 sharp rise, as you might imagine, after each  
18 vaccination, and sort of gradually rising to levels of  
19 doing 20 and 25 parts per billion in blood.

20 The two lines, one is for the very low bodyweight  
21 infants, three standard deviations below the normal,  
22 and the other is for the 95 percentile and that's -- A

1 key calculation in this is whether or not any excretion  
2 took place during this six-month period. There is no  
3 information on that with regard to humans. There is  
4 information with animals which suggests that they do  
5 not excrete methylmercury or inorganic mercury during  
6 the suckling period, and this is one of the big  
7 questions we have for humans, whether any excretion  
8 took place.

9 Here the calculation, just assume there was a dilution  
10 due to the growth of the baby, an increase in the  
11 volume of distribution of mercury. These levels of 20  
12 parts per billion are about the WHO upper safe limits  
13 for the general population. For EPA guidelines, they  
14 will be higher than this. I think the EPA guideline  
15 would give a blood level of about five or four parts  
16 per billion. So it depends which agency's point of  
17 view you take.

18 The toxic effects of ethylmercury on growing infants,  
19 as has been pointed out, is unknown, but with  
20 methylmercury effects have not been seen in populations  
21 at 20 or 25 parts per billion, but may have been seen  
22 at levels as low as 40. Thank you.

1       **DR. GREENBERG:** Thank you.

2       Do we have other questions?

3       **DR. GERBER:** Michael Gerber, NIAID. Let's see, I'm a  
4       little bit confused about your description of that  
5       report from Toronto and the neonates who died --  
6       neonates who died after the thimerosal exposure. You  
7       said on postmortem exam there was no pathological  
8       evidence of acute mercury toxicity. Did the authors  
9       believe that the mercury was the cause of death, or was  
10      there some other cause of death?

11      **DR. BALL:** It was not -- it was not mentioned. There  
12      was a -- The index case was one case that died  
13      suddenly, and they must have had some reason to examine  
14      mercury, because then they looked the previous 13  
15      infants who had omphaloceles treated with thimerosal,  
16      and -- and this is the -- and they came up with nine of  
17      them who had necropsies and got tissue mercury levels  
18      on those infants.

19      **DR. GREENBERG:** Dixie?

20      **DR. SNIDER:** Dixie Snider, CDC. Leslie, a very simple  
21      question: In the tables and the graphs I was looking  
22      at, I'm not clear on what's being compared. As I

1 recall your calculations -- but the micrograms you were  
2 coming up with were -- in thimerosal were micrograms of  
3 mercury.

4 DR. BALL: Exactly.

5 DR. SNIDER: The EPA, ATSDR, FDA limits, are they  
6 methylmercury?

7 DR. BALL: Methylmercury.

8 DR. SNIDER: So you're comparing mercury to  
9 methylmercury.

10 DR. BALL: Well, from thimerosal, it's ethylmercury.

11 DR. SNIDER: Since it's most --

12 DR. BALL: Right.

13 DR. SNIDER: But your calculations were actual  
14 micrograms of mercury?

15 DR. BALL: It's in the form of ethylmercury.

16 DR. SNIDER: So are you comparing ethylmercury to  
17 methylmercury or --

18 DR. BALL: Yes.

19 DR. SNIDER: -- ethylmercury to methylmercury?

20 DR. BALL: Ethylmercury to methylmercury.

21 DR. SNIDER: In micrograms?

22 DR. BALL: In micrograms.

1 DR. SNIDER: Okay. So, ideally, you would do moles --

2 DR. BALL: Right.

3 DR. SNIDER: -- but since that doesn't -- there's not  
4 much molecular weight difference, it's going to be  
5 close.

6 DR. MAHAFFEY: Kate Mahaffey, U.S. EPA.

7 The references for methylmercury is set assuming  
8 there's not a lot of exposure to other sources of  
9 mercury. Are the infants exposed to additional sources  
10 besides the vaccines? Because we know that they --  
11 those that are breast fed, at least, have an ongoing  
12 exposure to mercury from their mothers.

13 DR. BALL: Yeah, that's an excellent point. In the  
14 calculations, we were assuming no other exposures.  
15 And, in fact, infants are exposed to mercury from other  
16 sources, even infants that aren't eating tuna fish  
17 sandwiches, but maybe getting exposed through the  
18 breast milk, or, prenatally, have mercury levels, as  
19 you saw in the abstract, probably also related to  
20 either ingestion of fish in the mother or from dental  
21 amalgams.

22 DR. MAHAFFEY: And is there any effort to look at these

1 additional sources of mercury and incorporate them in  
2 the cumulative exposure to mercury that you've  
3 described from the vaccine?

4 **DR. BALL:** You know, there weren't any references that  
5 I was aware of that had good data on the alternative  
6 exposures. So I think that would require an effort  
7 with the various agencies that do have expertise in  
8 looking at those other exposures.

9 **DR. GERBER:** Gerber, NIAID. I just have a question for  
10 Dr. Clarkson.

11 When you were talking, you were talking in terms of  
12 parts per billion, but your "Y" axis was in micrograms  
13 per liter. Are you just assuming those are same thing?

14 **DR. CLARKSON:** That's the same, yes. Right.

15 **DR. ROGAN:** I'm Walter Rogan from NI Environmental  
16 Health Sciences.

17 As Dr. Plotkin pointed out, the choice of the  
18 denominator for time is kind of arbitrary and  
19 scientifically, I guess, it would depend on your model  
20 for how you think toxicity is occurring. And although  
21 I think it could be argued that toxicity is directly  
22 related to cumulative exposure, I think that for this

1 class of compound that, you could also make an argument  
2 that toxicity is related to peak excursion. So just an  
3 argument, it could be made to go in the direction of  
4 seven months, or eight months, or nine months. The  
5 argument could be made to go in the direction of one  
6 day and how high you got on the day of vaccination. So  
7 it's not a -- it's not a -- the sixth-month is not a  
8 maximum in terms of consideration of toxicity. It's  
9 just sort of an intermediate level that they, you know,  
10 chose to display.

11 **UNIDENTIFIED SPEAKER:** Dr. (inaudible) from CBER. Just  
12 a point of clarification. The EPA numbers are in  
13 micrograms per kilograms per day?

14 **DR. BALL:** Correct.

15 **UNIDENTIFIED SPEAKER:** And in your calculations, how  
16 did you -- I'm not clear on how you looked at the  
17 bodyweight of the babies.

18 **DR. BALL:** Ours were in total micrograms. And they  
19 were total micrograms, but -- and then when we did the  
20 calculations, we used the weights for the 5th  
21 percentile, 50th percentile, 95th percentile. So we  
22 took into consideration the weight of the infant.

1 **UNIDENTIFIED SPEAKER:** So one of the percentiles was  
2 about 400 micrograms. That was micrograms per kilogram  
3 bodyweight?

4 **DR. BALL:** That was the maximum -- Are you talking  
5 about with the guidelines, the graph on the guidelines?

6 **UNIDENTIFIED SPEAKER:** Yes.

7 **DR. BALL:** Those calculations were based on the total  
8 safe intake that you would calculate for that weight of  
9 infants. So if it was, for example, 5th percentile  
10 infants, you would use that weight to reach that total  
11 maximum level, using the analogous EPA, ATSDR, or FDA  
12 standards or guidelines.

13 **UNIDENTIFIED SPEAKER:** That wasn't clear in the  
14 presentation. Thank you.

15 **DR. GREENBERG:** We have a minute left for a quick  
16 question.

17 **DR. MYERS:** Martin Myers, NVPO.  
18 Leslie, just in your review, what proportion of  
19 vaccines in the first six months are actually  
20 distributed in multi-dose vials?

21 **DR. BALL:** I think that CDC has those data and will be  
22 presenting those this afternoon.

1 **DR. GREENBERG:** We now have thirty seconds for one more  
2 question. Last question.

3 **DR. FISHER:** Yes. Barbara Lowe Fisher with the  
4 National Vaccine Information Center.

5 I'd just like to congratulate the FDA on performing  
6 this analysis and for taking the action that it did to  
7 ask the manufacturers to take thimerosal out of the  
8 vaccines. I think that the public expects a strong and  
9 effective FDA, and that this kind of action, where it  
10 may temporarily cause questions about vaccine safety,  
11 in the long run, it's going to instill confidence and  
12 trust in vaccines and in the system.

13 I have one question. On your total of 187.5 for the  
14 vaccines in the first six months that are given, you  
15 used DTaP, three doses for DTaP for American infants.  
16 What would the total be if DPT were used, because some  
17 infants are still getting DPT?

18 **DR. BALL:** It's the same.

19 **DR. FISHER:** The same thing?

20 **DR. BALL:** The same amount.

21 **DR. GREENBERG:** Okay. On that note, I'll call the  
22 meeting to an end. I'd like to thank all the speakers

1 who did a great job.

2 Now, you have one hour for lunch, so you have to be  
3 back here at 1:00.

4 (LUNCH RECESS FROM 12:00 NOON TO 1:04 P.M.)

5 **DR. GREENBERG:** Well, this afternoon we're moving onto  
6 a couple of other important areas, and the first is  
7 going to be the organomercurials, and we have two  
8 substantial talks. The first is by Dr. George Lucier,  
9 who is the Director of the Environmental Toxicology  
10 Program at the NIH, and he's going to talk to us about  
11 "Ethyl and Methylmercury: Pharmacokinetics and  
12 Toxicology."

13 **DR. LUCIER:** Thank you. I think. Actually, this  
14 invitation to speak here was accepted by my office  
15 staff when I was vacationing and camping in the  
16 Adirondacks and not accessible to any phone. So Martin  
17 coerced my office staff into me accepting this, but I'm  
18 glad they did. I think it's an appropriate activity  
19 for me to participate in.

20 I believe the reason that I was asked to give this  
21 presentation is that beginning in 1997 -- I should  
22 point out, first of all, that I'm not a mercury

1 researcher, although I did have a couple of papers back  
2 in the early 1970s. I have a research group, but it's  
3 in receptor-mediated talks against dioxins and  
4 estrogens and so forth. But my involvement with  
5 methylmercury emerged in 1997 when I was asked to chair  
6 an interagency review of EPA's report to Congress,  
7 which, of course, was due in the end of 1997. I was  
8 assured that this activity would only last two months.

9 But while this was going on, ATSDR released a draft  
10 toxic profile. Phillippe Grandjean published his papers  
11 in neurobehavioral changes observed in the Faroe Island  
12 children exposed prenatally to methylmercury, and a  
13 number of other activities emerged that really called  
14 for attempts to harmonize across federal agencies what  
15 the science was telling us and what it wasn't telling  
16 us regarding methylmercury, particularly as it relates  
17 to developmental neurotoxicology.

18 These activities led to a workshop that we had in North  
19 Carolina in 1998, the fall of 1998, about eight or nine  
20 months ago. In that, we addressed in a very rigorous  
21 way the major studies that had been used in health  
22 assessments for methylmercury toxicity. We had

1 remarkable cooperation from the interagency committee,  
2 including EPA, ATSDR, FDA, NOAA, the relevant parts of  
3 CDC, and other agencies as well and equally remarkable  
4 cooperation from the major investigators who's studies  
5 we were reviewing. Tom Clarkson, who's here, and  
6 showed one of his overheads this morning, which I  
7 thought was particularly insightful, as well as  
8 Phillipe Grandjean and Donna Merguler, who is  
9 conducting some studies in the Amazon.

10 That's my name and where I'm from. My presentation  
11 will be, in a sense, two parts. And the first part is  
12 a summary of the interagency activities that we've had  
13 regarding methylmercury, particularly the areas of  
14 agreement and the findings that emerged out of our  
15 workshop in 1998.

16 And the second is what we know, and that's written very  
17 small, it probably should be written smaller, and don't  
18 know About ethylmercury." That'll be a shorter part of  
19 the presentation because, as you heard this morning  
20 from a number of the speakers, there just isn't too  
21 much information out there on ethylmercury. I'll  
22 discuss a few issues that perhaps weren't presented

1       this morning.

2       The purpose of the workshop was to discuss and evaluate  
3       the major studies, epidemiologic studies, associating  
4       methylmercury exposure with an array of developmental  
5       measures in children. It was in response to the  
6       requirement that the emerging data from the Seychelles  
7       and Faroe Islands undergo a level of scrutiny beyond  
8       journal peer review if they are to be used in policy  
9       setting.

10       So, keep in mind, this was an extraordinary rigorous  
11       review in such a way that I think is rarely done in  
12       terms of individual papers. This workshop involved  
13       presentations by the groups who were conducting the  
14       studies, really a barrage of questions about what they  
15       did, how they did it, how they analyzed the data,  
16       information that really isn't found in the published  
17       literature, and can't be found, because the journals  
18       would never allow publication of that volume of  
19       information.

20       This was really done under the impetus of the White  
21       House Science Office, the Office of Science Technology  
22       Policy. Fran Sharples (phonetic) there was the point

1 person. It involved a number of different agencies  
2 shown here. I hope you can read it okay. A number of  
3 institutes, agencies within DHHS; the NIEHS, which is  
4 where I'm from, Bill Raub's Office of the Assistant  
5 Secretary for Planning and Evaluation, and, of course,  
6 he'll give the next presentation and share the panel  
7 discussion; parts of CDC; ATSDR; FDA; again EPA; NOAA;  
8 OSTP; and also the Office of Management and Budget who  
9 was involved in this.

10 So you should keep in mind, as I go through what I'm  
11 going to say, in terms of the points that I make,  
12 they're really not my points. It's really the points  
13 of this interagency activity that basically was  
14 approved by all these various agencies and, in a sense,  
15 also approved by the major investigators whose studies  
16 we were reviewing, and generated by the reports, sub-  
17 reports, that were prepared by each of the panels, and  
18 I'll get to those later.

19 First of all, a number of key issues that we kept in  
20 mind as we went through the interagency deliberations.

21 I think it's important to point out here that we hear  
22 a lot about interagency differences, particularly in

1 regards to the methylmercury issue. It is clear that  
2 we do differ. Agencies do differ in some respects, but  
3 there are much more areas of agreement than there are  
4 areas of disagreement, and let me go through some of  
5 these issues that we are cognizant of before the  
6 workshop began.

7 One, methylmercury is a developmental neurotoxin in  
8 people. There's multiple publications, from Minamata,  
9 Iraq, and others to document that. The developing  
10 fetus is roughly ten times more sensitive than adults.

11 This is a rough estimate, but probably not too bad of  
12 one. I think Tom Clarkson made that original estimate,  
13 and from my read of literature it can't be too far off.  
14 The relative sensitivity of infants to methylmercury is  
15 unknown, but they are likely more sensitive than  
16 adults. We really don't have information in infants.  
17 We have to keep in mind that the central nervous system  
18 and the brain is still undergoing assembly and it's  
19 likely it would be sensitive to toxic insult, but we  
20 really have very little information, nothing near the  
21 extent that we have for prenatal exposures of the  
22 developing fetus and also for adults. We just don't

1 have much for infants.

2 Effects -- This is a no-brainer. Effects at low-level  
3 exposures are difficult to evaluate. Methylmercury is  
4 ubiquitous and nearly everyone has some exposure. Kate  
5 Mahaffey brought that point up in the question and  
6 answer to the last presentation, that virtually  
7 everyone in this room has some degree of methylmercury  
8 in their bodies. So any additional exposure that's  
9 received -- and infants have some as well through  
10 lactational exposures and other sources. Anything we  
11 receive is really an incremental exposure to what's  
12 already there. So we need to be especially cognizant  
13 of the issues related to cumulative health assessments  
14 from the multiple sources of methylmercury, mercury in  
15 vaccines only being one of them.

16 Finally, initial efforts to establish safe exposure  
17 levels acknowledge the need for further studies in  
18 populations with low levels of exposures. And that's  
19 really what led, back in the 1990s to early 1990s,  
20 funding for the studies in the Seychelles and the Faroe  
21 Islands, because of a need to have this information  
22 after seeing that the developing fetus was really at

1 risk based on the data from Minamata and also from  
2 Iraq.

3 The workshop that we had was structured around the  
4 deliberations of five panels, and these are five panels  
5 that were basically external to the federal government.

6 I think of the 27 panelists that we had, I think there  
7 were only two representatives from the federal  
8 government on them. Walter Rogan from the NIHS was one  
9 of them, and he's here today and could perhaps help me  
10 answer some questions regarding the neurobehavioral  
11 endpoints.

12 But these are the areas that we felt that needed to be  
13 addressed in a critical rigorous way regarding those  
14 major studies: exposure, neurobehavioral endpoint,  
15 confounders and variables, design and Statistics, and  
16 we also had a group looking at experimental studies,  
17 studies in rodents, studies in monkeys, to see whether  
18 or not the experimental models were similar to what we  
19 were seeing -- gave results similar to what we were  
20 seeing in people. If that's the case, then it gives us  
21 more confidence in using those experimental studies in  
22 public health assessments.

1 Major studies that we looked at was Iraq, where the  
2 consumption of bread prepared from wheat seed treated  
3 with methylmercury fungicides; the Seychelles, the  
4 consumption of fish as a significant source of dietary  
5 protein; and the Faroe Islands, where the consumption  
6 of pilot whale meat which contains higher levels of  
7 methylmercury than local fish. I'll get back to the  
8 importance of some of the consumption habits in a  
9 minute or two.

10 These are the outcomes, and I hope you can read that  
11 okay. I recognize that it's somewhat small.

12 In Iraq, affected individuals consume 50 to 400  
13 milligrams of methylmercury over six months. Motor  
14 retardation was seen in infants born of mothers with  
15 hair levels in the 10 to 20 part per million range.  
16 Now, there were effects seen at much higher levels,  
17 obviously, but this was as low as the evaluations could  
18 get, and maybe Tom Clarkson in his comments could  
19 elaborate on that if necessary.

20 We really spent the bulk of the time in the Seychelles  
21 and the Faroes. In the Seychelles, infants were born  
22 of mothers with mean hair levels of 6.8 parts per

1 million, the range of .5 to 27. No developmental  
2 effects were detected using standardized measures of  
3 global neurological function in children up to 66  
4 months of age. There is also prior looks at  
5 developmental aspects, I think, at 29 months of age as  
6 well.

7 In the Faroe Islands, infants were born of mothers with  
8 mean maternal hair levels of 4.3 parts per million,  
9 very similar to what was observed in the Seychelles, in  
10 a similar range. They also had mean cord blood  
11 concentrations, and I just noticed looking at this that  
12 it's not parts per million, that it's parts per  
13 billion. So the range of 22 parts per billion, a range  
14 of .9 to 351. Quite a broad range.

15 The Faroe study assessed the main specific effects,  
16 which are different than the global measures in  
17 neurological function. Test of memory, attention, and  
18 language were negatively associated with methylmercury  
19 exposure in children up to 84 months of age. So these  
20 kids were 84 months of age and 66 months of age, up to  
21 66 months of age in the Seychelles. It's important to  
22 note that the follow-ups continue in both of these

1 studies with Tom Clarkson's group, as well as with  
2 Phillipe Grandjean in the Faroe Islands.

3 Well, why is the Seychelles study negative and the  
4 Faroe study positive? That was a big question for the  
5 workshop, and I'm going to not present all the  
6 information, but I'm going to briefly go over some  
7 issues relative to exposure, study design, confounders,  
8 and data analysis that could possibly account for the  
9 differences.

10 In regards to exposure, we had quite a bit of  
11 discussion about cord blood versus hair levels, but I  
12 think the overriding conclusion of the panel was that  
13 hair levels are a pretty good marker of methylmercury  
14 exposure. Cord blood is a good marker as well. Each  
15 of them have their advantages and disadvantages, but  
16 there's a wealth of literature now on hair levels of  
17 methylmercury as a marker of exposure.

18 I was just reading in the, flying up here this morning,  
19 USA Today, and there was an article about Andrew  
20 Jackson and why he died, and some people, I guess, had  
21 theorized -- I hadn't known that -- that he had died of  
22 mercury poisoning. But 200 years later, nearly 200

1 years later, they analyzed his hair and found there's  
2 not enough mercury in Andrew Jackson's hair to account  
3 for his death. So it has to be a pretty good marker of  
4 exposure to be used 200 years later to help ascertain  
5 the cause or what was not the cause of death in the  
6 case of Andrew Jackson.

7 The second issue was -- And this one I think was  
8 particularly important and may be relevant to the  
9 vaccine issue -- exposure in the Faroes was considered  
10 to be more episodic than in the Seychelles. In the  
11 Faroes, basically, there's about one pilot whale meat  
12 meal consumed per month, maybe one to two fish meals  
13 consumed per week. In the Seychelles, I think it was  
14 something like ten meals or so of fish that were  
15 consumed per week. So it was a much more spiked  
16 exposure, if you could look at it that way, in the  
17 Faroes as compared to the Seychelles. Many of the  
18 panelists in our review groups felt that this is  
19 possibly an important factor in accounting for the  
20 differences in results between the Faroes and the  
21 Seychelles, particularly when you consider that we're  
22 looking at windows of sensitivity for the developing

1 nervous system.

2 Third, exposure response relationships were based on  
3 surrogate markers and hair or blood concentrations in  
4 fetal and children's brains can only be estimated.  
5 While this is true, I think for the reasons that I've  
6 said before, I think we have a wealth of information  
7 about exposure and what it means in terms of hair  
8 levels, not that we can't get more, but I think that  
9 information was pretty good. It was not considered a  
10 major problem or a major reason by the panelists for  
11 the different results between the Faroes and the  
12 Seychelles.

13 Now, getting to the study design issues, there was one  
14 here actually was left off of the slide that should  
15 have been first, and that's the neurobehavioral  
16 endpoints. As I had mentioned earlier in the outcome  
17 slide, the Seychelles Islanders were monitored for more  
18 global measures of neurological function, whereas the  
19 Faroes were looked at for more domain-specific effects:  
20 memory, attention, language, these sorts of things.  
21 Many of the panelists felt that these were like  
22 comparing apples and oranges, and I think everyone on

1 the interagency committee and the scientists themselves  
2 agreed that they were really measuring different  
3 endpoints of neurobehavioral function. So this could  
4 very well explain the differences.

5 It's important to note that in the follow-up studies  
6 that are being conducted, there will be great effort  
7 made to measure common endpoints in those children, who  
8 are, of course, getting older and older, and also to go  
9 through some of the same analytical processes that also  
10 exhibited some differences between the two studies in  
11 terms of analysis of the data sets.

12 Another one that was discussed in great detail:  
13 selection bias. This was a potential concern in the  
14 Seychelles studies because some individuals -- I think  
15 39 or something of the 79 -- were excluded because of  
16 debilitating conditions. Thorough analysis of that  
17 suggests that the selection bias was really not an  
18 issue in explaining the results. The panel, I think,  
19 felt almost unanimously on that issue.

20 Effects of culture and language were discussed in terms  
21 of the questionnaires, usually going back and forth  
22 between English, Creole, and French, and Scandinavian

1 in the Faroes study. Again, the panelists felt that  
2 this was not a major issue.

3 The age of testing, the panelists, on the other hand,  
4 felt that this was potentially an important issue,  
5 because at 66 months of age, there's a lot more  
6 variation among normal individuals in the -- those  
7 parameters that were assessed. In other words, there's  
8 a lot of noise in the system and it might be difficult  
9 to pick up an effect if one was present. And, again,  
10 continuing to follow up these kids at the later ages  
11 will help address that issue, but that was an area of  
12 potential importance that was earmarked by our review  
13 groups.

14 Order effects and effects of tests administration, as I  
15 recall, in the Seychelles study they gave the same  
16 order to each of the individuals in terms of the  
17 administration of the test. In the Faroes, I think  
18 they had four predetermined orders of how the tests  
19 were administered, and that wasn't really controlled  
20 for or dealt with in the model analyses that evaluated  
21 the results. So this was a potential issue of concern  
22 that the panelists raised regarding the Faroes data.

1 Confounders and data analysis issues, in the case of  
2 the Faroes, PCB exposures were also occurring. As most  
3 of you know, PCBs are also developmental  
4 neurotoxicants. They affect some of the same  
5 parameters as methylmercury effects regarding the  
6 developing nervous system.

7 The PCBs were measured in both the Faroes and the  
8 Seychelles. There was significant PCB exposure in the  
9 Faroes, essentially none in the Seychelles. So it's a  
10 potential confounder for Faroes but not the Seychelles.

11 The neurobehavioral endpoints subgroup of the panel  
12 said that they did not feel that the PCBs could -- are  
13 really confounding the results that were observed, even  
14 though they could have some effect on them.

15 Selenium, I knew selenium was a messy issue going in,  
16 and it still is. Some people think it affects one way,  
17 other people think it affects the other way, but  
18 everyone agreed that it would be important to use that  
19 as part of the analyses of the data, and that wasn't  
20 done.

21 Likewise, a number of dietary nutritional factors, the  
22 omega-3 fatty acids, which are beneficial to brain

1 development need to be looked at in subsequent studies,  
2 as well as a number of nutritional and dietary data  
3 that really weren't collected in the studies that have  
4 been published to date.

5 Genetic differences is potentially important. There  
6 may be ethnic differences in responsiveness, but given  
7 our lack of information about mechanism of action for  
8 developmental neurotoxicity for methylmercury, or PCBs  
9 for that matter, we're really not in a good position of  
10 pinpointing particular differences in gene activation  
11 pathways and so forth, that could possibly account for  
12 these differences.

13 Influence of covariants, in general, the panel felt  
14 that the Seychelles tended toward a slight  
15 overcontrolling and the Faroes a slight  
16 undercontrolling. Some particular issues that were  
17 raised were maternal smoking, which even though 40  
18 percent of the women smoked in the Faroes, this was not  
19 controlled for in the analysis.

20 Birth weight, that was controlled for in the Seychelles  
21 study, but birth weight could be associated with a  
22 methylmercury exposure in the development effects. So,

1 perhaps, that could have influenced the results and  
2 minimized the ability to detect an effect if it was  
3 there.

4 Town versus rural residence wasn't accounted for in the  
5 Faroes study.

6 To make a few brief points about the studies in  
7 experimental animal models, basically, they were in  
8 pretty good concordance, both qualitatively and  
9 quantitatively, with what was seen in people. There  
10 have been effects of methylmercury and effects of PCBs  
11 in the sensory system, motor function, and cognitive  
12 deficits, but at this time it's not possible to  
13 differentiate the effects of PCBs and neurodevelopment  
14 from effects of methylmercury in experimental animals  
15 mostly because of the lack of mechanistic information.

16 We have to keep in mind that in this situation, we  
17 have a very rich data set, at least for us who do  
18 environmental kind of exposures think it's rich, and  
19 it's extraordinarily rich regarding exposure and  
20 extraordinarily rich regarding response. What we don't  
21 know is what's happening in between in terms of the  
22 critical cellular steps that may be involved in

1 producing the neurological effects that may be seen,  
2 the migration of critical neurons and so forth, and  
3 that's an area of research that would yield great  
4 benefit to the public health assessments of both  
5 methylmercury and PCBs.

6 There are five panel recommendations and findings that  
7 emerged out of the workshop, and I'll go through them  
8 one by one. Again, this was agreed upon by all the  
9 participating agencies, the panel, and also the major  
10 study groups out of the Seychelles and the Faroes.

11 1. Methylmercury is a developmental neurotoxin, but  
12 effects -- We still got the same sentence in here -- at  
13 low does encountered by eating fish are difficult to  
14 evaluate. Not too much progress there, but certainly a  
15 strengthening of that statement.

16 2. All the studies reviewed were considered of high  
17 scientific quality and the panel recognized that each  
18 of the investigators had overcome significant obstacles  
19 to produce important scientific information. That was  
20 uniformly felt throughout the panels. We felt that a  
21 continued funding of these studies is necessary for the  
22 full potential to be realized. It's particularly true

1 for the Faroes and Seychelles, which are currently  
2 assessing developmental effects of methylmercury in the  
3 fish-eating populations, of course. The developmental  
4 studies would benefit by evaluation of common endpoints  
5 using similar analytical methods. And we noted that  
6 the Amazon study, although positive results were seen,  
7 did not look at developmental endpoints. A later study  
8 out of Grandjean's group that's just been published has  
9 looked at the Amazon studies where methylmercury  
10 exposure occurred through gold mining, and those  
11 results were positive as well in terms of visual-evoked  
12 potentials and some other measures of neurological  
13 function, following prenatal as well as post-natal  
14 exposure.

15 3. Results from the Faroes and Seychelles studies are  
16 credible and provide valuable insights into the  
17 potential health effects of methylmercury.

18 4. Some differences are clearly present in the  
19 results of the studies, but the panel was unable to  
20 clearly identify the sources of these differences.  
21 Among possible sources are the different effects of --  
22 Again, coming back to this one -- episodic versus

1 continuous exposure, ethnic differences, a lack of  
2 common endpoints in the Faroes and Seychelles studies -  
3 - A very important one, of course -- and several other  
4 confounders or modifying factors such as those found in  
5 the diet, lifestyle, as well as chemicals present in  
6 seafood, which is a source of methylmercury to these  
7 populations.

8 The other chemical constituents that may be explanatory  
9 include those that may be beneficial to fetal  
10 development, like the omega-3 fatty acids, and those  
11 that may be harmful to fetal neurodevelopment, such as  
12 the PCBs.

13 5. These studies have provided valuable new  
14 information on the potential health effects of  
15 methylmercury, but significant uncertainties remain  
16 because of issues related to exposure, neurobehavioral  
17 endpoints, confounders and statistics, and design.

18 If anyone wants to get a copy of the whole report, you  
19 can send me an e-mail. It's Lucier@NIEHS. That's L-u-  
20 c-i-e-r@NIEHS.NIH.GOV.

21 There has been a few publications I mentioned that have  
22 come out since we've had the report, and maybe Tom

1 Clarkson will give us an update of what's going on with  
2 his group as well in terms of recent publications.  
3 These are mostly from the Grandjean group and they  
4 involve the one shown here in terms of the Amazon  
5 study, which I mentioned; a paper -- another paper from  
6 the Faroe Islands on the delayed evoked potentials in  
7 children exposed to methylmercury from seafood; a paper  
8 with Murata as the first author and Grandjean the last,  
9 evoked potentials in Faroese children prenatally  
10 exposed to methylmercury; and another one that examined  
11 hypertension, a reported increase in hypertension in  
12 the kids exposed to methylmercury, also in the Faroe  
13 Islands. This paper, I believe, now is in press. It  
14 was presented at that Rio De Janeiro meeting in May of  
15 this year.

16 Ethylmercury or Thiomersal? You'll notice I'm using  
17 the European spelling, because it was in the reprints I  
18 had, so I used that spelling.

19 Now, I'll make a few points here that I think most of  
20 them have already been made, maybe some of them  
21 haven't, regarding ethylmercury and possible  
22 comparisons with methylmercury.

1 Exposure. Depending on the vaccination schedule and  
2 bodyweights, a two-month-old infant receives a bolus  
3 injection of 3 to 18 micrograms per kilogram. This was  
4 information I got by Bill Raub via Neal Halsey, and I  
5 assume that those calculations are correct. They seem  
6 similar to what was presented later on this morning, so  
7 I believe they're roughly correct.

8 This dose of mercury on vaccination day is much higher  
9 than daily exposure in the Seychelles and the Faroes,  
10 although the total dose received from vaccines is less  
11 than the mean exposures in the Faroes and Seychelles.  
12 Infant mercury intake per day from dietary sources is  
13 estimated to average .05 micrograms per kilogram per  
14 day in a chronic exposure, and this would be primarily  
15 through lactation as well as some other sources. And  
16 there's a few pieces of information in the scientific  
17 literature that support that estimate of infant uptake  
18 of methylmercury, exposure to methylmercury.

19 Biological half-life, similar to methylmercury. This  
20 is a little bit different than what was said this  
21 morning. For methylmercury, it's 40 to 150 days, and  
22 this was based on a number of different studies that

1 have been presented. I think different agencies use  
2 slightly different numbers, but I think the average --  
3 Chris, would it be right, it's about 70 -- 60 or 70, in  
4 that range? The one study I got ahold of regarding  
5 thimerosal, or ethylmercury, came from a suicide  
6 attempt. This was published three years ago actually,  
7 in "Clinical Toxicology," and this one lived. He also  
8 got about 80 milligrams per kilogram of thimerosal, and  
9 the half-life -- and Chris (inaudible) had sent me this  
10 reprint on Friday. It was estimated that the half-  
11 life, the second phase of the half-life, which is the  
12 one we need to look at here, was roughly 40 days in  
13 this one individual who survived that episode. Of  
14 course, we don't know what a near-death experience does  
15 in terms of the physiological factors that govern half-  
16 life, so I wouldn't guarantee that that's the half-  
17 life.

18 The information that we have in total suggests that it  
19 might be slightly shorter than methylmercury. And  
20 there is really no definitive information on potential  
21 differences that I could uncover between infants,  
22 children, or adults regarding biological half-life. I

1 don't know, Katie, if you have some more information on  
2 that.

3 Metabolism -- And I think this was brought out in the  
4 presentations this morning -- that demethylation of  
5 methylmercury appears to occur more slowly than  
6 deethylation of ethylmercury. I think there's a  
7 growing body of knowledge that suggests that that is,  
8 in fact, true, and it's significantly different. In  
9 other words, the demethylation occurs much more slowly  
10 than deethylation in terms of the conversion to  
11 inorganic mercury.

12 What about the toxicity of ethylmercury or thimerosal?

13 Again, we talked about the adult squirrel monkey study  
14 today, which was -- this was adults again and not a  
15 developmental study. Again, significant conversion to  
16 inorganic mercury; high levels in the kidney, as was  
17 presented this morning; lower levels in the brain; and  
18 no evidence of toxicity. And the doses that were given  
19 were equivalent to 1 or 6 micrograms per kilogram per  
20 day.

21 A second study, which was not discussed this morning,  
22 is that adult male and female rats were administered

1 five daily doses of equimolar concentrations of ethyl  
2 or methylmercury by gavage and tissue distribution,  
3 neurotoxicity, and nephrotoxicity assessed. This was a  
4 Magos study in 1985 in the Archives of Toxicology. And  
5 the key points of that paper were: neurotoxicity of  
6 methyl and ethylmercury were similar, although higher  
7 levels of inorganic mercury were seen in the brains of  
8 ethylmercury-treated rats consistent with what we'd  
9 said about metabolism; and likewise, because of that,  
10 the renal damage was greater in the ethylmercury-  
11 treated rats. Unfortunately, neither time-course nor  
12 dose response was attempted in these studies, nor was  
13 any developmental studies attempted.

14 And after having said that, there are a number of  
15 critical toxicology studies that could be conducted to  
16 address some of the uncertainties that -- and you  
17 probably all know about and we talked about this  
18 morning. Unfortunately, all of these take time and,  
19 you know, clearly, if we embarked upon these studies  
20 now, we're not going to have results until long after  
21 some of the initial and significant decisions have to  
22 be made regarding the vaccine program. I think we have

1 to acknowledge the paucity of data and move forward  
2 with the decision-making process, but I think it's good  
3 to think about what knowledge gaps do exist that really  
4 limit our ability to make those assessments in a way  
5 that we would like to make them.

6 Developmental neurotoxicity, we need to assess those  
7 response and age dependent responses in appropriate  
8 systems. We need to, for the reasons I discussed  
9 earlier regarding the PCBs and methylmercury, look at  
10 mechanistic studies, and we need to focus on critical  
11 changes in gene function and cellular pathways. In all  
12 the toxicology studies we do in the national toxicology  
13 program, and we do 30 or 40 of these a year as part of  
14 that interagency program, we're starting to take  
15 increasing advantage of the human genome project and  
16 what that allows us to do in terms of looking at  
17 patterns of gene expression following exposure to  
18 various toxicants to compare potency of different  
19 agents and also mechanism of action, as one agent going  
20 through a similar mechanism of action as another agent.

21 That might be particularly relevant to the issues at  
22 hand for the ethyl/methyl issue.

1 Evaluation of possible sensitive subpopulations based  
2 on either genetic predisposition, diet, or cumulative  
3 risk. Again, we're exposed to other developmental  
4 neurotoxicants. Are they additive? Are they  
5 synergistic? Are they antagonistic towards each other?

6 Do they block each other's effect? And biomarkers of  
7 exposure, including hair, need to be evaluated.

8 There are no studies in developmental toxicity that I  
9 was able to find in experimental models or people, and  
10 because of this, in my opinion, health assessments for  
11 ethylmercury at this time must assume that ethylmercury  
12 is producing the same effects at the same doses as  
13 methylmercury.

14 I couldn't help but to show a couple of slides here.

15 One of the things that I do in my own laboratory is  
16 work with biomathematicians to develop physiologically-  
17 based pharmacokinetic models, and this is a model that  
18 might be applied to a prenatal methylmercury study.

19 When you have various kinds of compartments in the  
20 maternal system and also the fetal system, looking at  
21 placental transfer. Of course, excretion in the  
22 maternal system, either through the urine or the feces.

1 Blood levels, relationship to hair levels, secretion  
2 in the milk, of course, when you're looking at  
3 lactational exposure post-natally.

4 And once you have some information regarding all these  
5 parameters, and it has to be done in an iterative way  
6 with generation of laboratory data, you can develop  
7 mathematical models that predict the movement of the  
8 chemicals throughout these various compartments. And  
9 once you can do that with your existing database, it  
10 gives you a great deal of confidence in extrapolating  
11 that model to expose your circumstances for which maybe  
12 you don't have data.

13 So I think these kinds of models are always very  
14 helpful in health assessments. And I know agencies  
15 such as EPA, ATSDR, and FDA use them extensively in the  
16 health assessments that they make. But in the case of  
17 the vaccine issue, we really have to look at it in  
18 terms of the infants and children issue, which we've  
19 discussed already, and I think the point has been made  
20 that we have information in adults, we have information  
21 in effects on prenatal development, and we have very  
22 little information about the relative sensitivity of

1 infants, either to adults or to the developing fetus.  
2 So we need to develop that type of physiological-based  
3 pharmacokinetic model, to look particularly at the  
4 issue of infants and children and how tissue  
5 concentrations might be related to the potential for  
6 adverse health effects.

7 I also pointed out that in the case of the  
8 biologically-based modeling, this is an iterative  
9 process. You don't just get yourself a mathematician  
10 friend and say "Do this model." They usually come up  
11 with some sort of model that is filled with flaws, and  
12 then you go back, and through additional experiments,  
13 start refining the model.

14 So you collect the data, refine the model, compare it  
15 to the existing knowledge base. You start circling  
16 through this thing a few times. By the time you get  
17 through it a few times, you're then in a position to  
18 use it in dose response assessment and quantitative --  
19 other aspects of quantitative risk assessment, but,  
20 again, these things take time. We're not going to both  
21 generate the data and generate these types of models,  
22 you know, within the next six months. It's going to

1 take some time to do that.

2 And finally, in case I -- I don't if I've -- I usually  
3 show this slide when I want to offend people. It's not  
4 that I want to offend anyone, but I show it when I give  
5 talks about risk assessment for environmental agents,  
6 and -- because we deal with a lot of different types of  
7 folks in terms of evaluating what we should do and  
8 shouldn't do in risk assessment. And these are meant  
9 to be caricatures. They certainly don't reflect anyone  
10 in this room, I'm sure.

11 (LAUGHTER)

12 **DR. LUCIER:** But, you know, some of my favorite, of  
13 course, are molecular biologists, you know, you're  
14 stupid, I'm smart. I actually know a lot of molecular  
15 biologists that aren't smart.

16 (LAUGHTER)

17 **DR. LUCIER:** And of course you have mathematicians that  
18 think an equation like this can give us truth. And it  
19 helps, but certainly not by itself.

20 Regulatory official, that's definitely not true in this  
21 room. I tell you, the interagency group that I worked  
22 with in this was absolutely terrific. But one

1 caricature would be, "Don't trouble me with science."  
2 Industry, "Positive results are meaningless." And  
3 environmental activists, "If it's chemical, it's bad."  
4 Lawyer, do we have any lawyers here?

5 (LAUGHTER)

6 **DR. LUCIER:** I heard a joke about lawyers the other  
7 day, that 99 percent of the lawyers give the other 1  
8 percent a bad name.

9 (LAUGHTER)

10 **DR. LUCIER:** And as a result of all this, frequently  
11 the public health decisions that come out of the  
12 federal government, because of these various  
13 caricatures, really aren't believed and the public  
14 doesn't trust us. So I feel very good about this  
15 workshop because, I think, as was stated in the  
16 original goals that the purpose, to get all the  
17 information out on the table, what we know and what we  
18 don't know, do it in an open context where people can  
19 comment, add to it, subtract from it, and so forth, I  
20 really think is the way to go about this.  
21 So I appreciate the invitation and the opportunity to  
22 participate. Thank you.

1 (APPLAUSE)

2 **DR. GREENBERG:** Thank you, George. We have some time  
3 for some questions. Too much data for you, huh?  
4 Dixie?

5 **DR. SNIDER:** Dixie Snider, CDC.

6 You indicated that the mechanism by which methylmercury  
7 might be exerting its neurotoxic effects is unknown.  
8 Are there any reasonable hypotheses in your mind? And  
9 how would that relate to ethylmercury and methylmercury  
10 with regard to mechanism?

11 **DR. LUCIER:** You know, there's some information  
12 available -- And, again, I'm not a neurochemist or a  
13 neurotoxicologist, so maybe some of the other folks who  
14 have looked at this on the panel could add to my  
15 answer. But there have been effects shown on various  
16 constituents that are involved in their own migration  
17 and other aspects of neurodevelopment. I don't think  
18 there's anything that people would say, "Aha, I think I  
19 understand what that critical event is that's producing  
20 the toxicity."

21 You don't have to know all the steps that are involved,  
22 but what you really want to know is what the key

1 critical event is or the mode of action is, and once  
2 you have that information, you're on much better  
3 footing in which to compare and predict responses that  
4 might be occurring across the chemical class.

5 Say, for example, it was done with the environmental  
6 estrogens or the dioxins where we knew the mode of  
7 action was receptor mediated -- Let me talk about  
8 something I know something

9 about -- we're then able to take classes of chemicals and  
10 see how well they interacted with that system and  
11 produced a specter of deemed changes that are  
12 associated with it and use that information in  
13 regulatory decision-making in terms of determining  
14 which of these dioxin analogues or which of these  
15 environmental estrogens are the ones we need to be  
16 worried about.

17 And if we had the same sort of analogy with the  
18 methylmercury and PCBs, we would be able to go much  
19 further in that type of comparison.

20 **DR. GREENBERG:** Gina, did you have a question?

21 **DR. RABINOVICH:** You stated -- And I'm questioning this  
22 because I'm not sure I understand it or if anybody else

1 in the room does also. You stated that the  
2 demethylation of methylmercury appears to occur more  
3 slowly than the deethylation of ethylmercury.

4 Can you expand on the implications of that? Is that  
5 good or is that bad?

6 **DR. LUCIER:** Well, you know, I wish -- I'd like to say  
7 I knew, but I've heard that it's good and I've heard  
8 that it's bad.

9 (LAUGHTER)

10 **DR. LUCIER:** I've heard that it's good because this is  
11 a detoxication step in some respect. Say, in terms of  
12 the kidney, it's a way of, you know, getting the  
13 mercury out of the body. And I've also heard -- But  
14 since we don't know how methylmercury works, we're at a  
15 little bit of a loss to make too much of a definitive  
16 statement. I've heard from others that maybe it  
17 creates a mechanism for retention of mercury in the  
18 brain as the inorganic mercury is then -- does not  
19 retrograde cross the blood/brain barrier. So it's a  
20 mechanism retaining mercury in the brain.

21 So, I don't know. I think it's a real finding . . .  
22 and I think it's an important finding, but I don't know

1 how to quite put it in the context of the comparative  
2 toxicity issue.

3 I think it is important to note from the Magos study,  
4 in which he directly compared ethyl and methylmercury,  
5 that he found essentially the same results in both  
6 studies, with the exception that the renal toxicity was  
7 greater with ethyl, and I think that was because of the  
8 demethylation as a way of concentrating the mercuric  
9 chloride or inorganic mercury in the kidney.

10 **DR. RABINOVICH:** Okay.

11 **DR. PLOTKIN:** Let me try to frame this question  
12 intelligently if I can.

13 In analyzing the Faroe Island data, which are the  
14 positive set of data, in thinking about -- at least in  
15 thinking about microbiology, one can usually calculate  
16 a 50 percent dose, that is, to say a dose that caused a  
17 reproducible effect 50 percent of the time.

18 Now, from my reading of the Faroe Island studies, there  
19 is no level in those studies that had a 50 percent  
20 effect, but there are mathematical ways of trying to  
21 predict the 50 percent effect.

22 So my question, if it is a question, is: Can you

1 calculate from the Faroe Island study what is the 50  
2 percent effective dose, either in terms of hair level  
3 or blood level of mercury?

4 **DR. LUCIER:** And since -- You know, you are in much  
5 better shape to do that when you're interpolating  
6 within your data set, rather than extrapolating outside  
7 of it.

8 The Faroes data doesn't have adequate information  
9 within it to define a slope down in that low-dose  
10 region. Now, in the absence of that type of data, one  
11 can use various types of models to extrapolate to an  
12 EC-50 concentration using some of the parameters  
13 already looked at. Several assumptions would have to  
14 be made, but my guess is any extrapolation of that  
15 nature, because of the nature of the data set, would be  
16 highly subject to debate and criticism because of the  
17 assumptions that would have to be made.

18 But I think -- I think the effort itself may be a  
19 worthwhile one, and then point out sort of what the  
20 uncertainties are with that estimation.

21 **DR. HALSEY:** You mentioned that we don't understand --

22 **DR. GREENBERG:** Identify yourself?

1       **DR. HALSEY:** Neal Halsey. I'm sorry.

2       You mentioned that we don't understand the mechanism by  
3       which the neurotoxicity occurs, and we also don't know  
4       what the relative sensitivity of the infant is, which  
5       is what we are all concerned about right now.

6       I'm wondering if there's any information that might be  
7       applicable or might help educate us with regard to the  
8       slope of the curve for other developmental neurotoxins.

9       There's lead, there are others. We -- I don't think  
10      this audience knows what those slopes look like, and  
11      whether you think they may be at least informative.

12     You can't necessarily apply them directly to mercury,  
13     but it would help to try to get some estimate of what  
14     the relative increase in toxicity for an infant is at  
15     birth, at two months, as compared to at six months or  
16     at twelve months.

17     Where does -- What is the shape of those curves of  
18     change in the neurotoxicity from other products?

19     **DR. LUCIER:** Yeah. That's -- I think that's a great  
20     point, and I'm not a neurotoxicologist again, so I  
21     don't have that information at hand. We have -- We've  
22     analyzed through the NTP a lot of chemicals in our

1 neurotoxicology batteries. So maybe it would be  
2 worthwhile for me to go back and ask those folks to  
3 look at that particular issue and see what comes out of  
4 it.

5 And many of these, of course, are assumed to have  
6 threshold effects, that there will be a dose below  
7 which no effect would occur. My guess is -- And this  
8 is a guess, so take it for what it is -- that you'll  
9 still get a variety of dose response curves because  
10 there are multiple mechanisms of developmental  
11 neurotoxicity. I presume that some would drive it very  
12 steeply and others would drive it in a more shallow  
13 sense, but I don't know that for sure, Neal.

14 Did you have something to add to that, Katie?

15 **DR. MAHAFFEY:** Yeah. Speaking for --

16 **DR. GREENBERG:** Identify yourself, and why don't you  
17 step up here and use the mic.

18 **DR. MAHAFFEY:** I'm Kate Mahaffey with EPA.

19 Looking at inorganic lead, you can get an interesting  
20 comparison because the occupational levels that are  
21 considered acceptable are more in the range of 40 and  
22 50 micrograms per deciliter, with reproductive effects

1 certainly at lower levels.

2 There's also a body of literature showing sort of  
3 neuropsychological changes at around 25 to maybe 40  
4 micrograms per deciliter as a blood level. For the  
5 infant and young child, the levels which effects are  
6 found are certainly less than 10 micrograms per  
7 deciliter, with some studies finding effects below 10.

8  
9 These effects are sustained in that when these levels  
10 were observed in children and the children followed two  
11 decades, or 15 years later, as adolescents, adverse  
12 effects of lead were still seen, which sort of argue  
13 for infant/young child changes at perhaps the fourth to  
14 a fifth, the levels that affect adults, which is not  
15 really dissimilar from what some of the people who have  
16 studied mercury experimentally and some of the European  
17 agencies who have done regulatory evaluations on  
18 mercury are suggesting is the ratio between effects in  
19 the young child or -- I'm sorry, effects in the fetus  
20 and effects in the adult.

21 So I think it's kind of roughly in that range, but it's  
22 really the type of effect you're looking at and,

1 certainly, a lot of variability within individuals.

2 **DR. RABINOVICH:** I guess to follow-up one question to  
3 either of you -- I'm Gina Rabinovich, NIAID -- Is it  
4 appropriate at this point in the discussion to be using  
5 the word "mercury" versus methyl or ethyl? Do we  
6 accept that methyl is the appropriate model for what's  
7 going on in the infant? And you were talking about  
8 mercury. Is that relevant, you think, to both?

9 **DR. MAHAFFEY:** I think George's views, that given our  
10 limited information on ethylmercury, that methylmercury  
11 appears to be the closest chemical species we have to  
12 do that. And so it is a matter of where you want to go  
13 with the kind of uncertainty that's there.

14 **DR. LUCIER:** My statement was based on assumption, not  
15 convincing scientific evidence, because it's not  
16 convincing evidence that tells me that they're acting  
17 identically. There's some evidence, or similar. My  
18 statement on using -- treating ethyl as methyl was  
19 based on really the lack of information, and given that  
20 lack of information, that's the assumption we would  
21 have to make. It might be after we generate more data  
22 we're willing to say, "Hey, there's some key

1 differences here," that we need to treat it  
2 differently.

3 **DR. RABINOVICH:** Given that statement, when you  
4 describe an infant mercury intake per day from dietary  
5 sources, this is all mercury, all forms, or this is  
6 methylmercury? Because you stated that the exposures -  
7 - dietary exposures is estimated to be .05 microgram  
8 per kilo per day, which maybe present a number that  
9 looks like we know, we measured it, we know what's  
10 going on.

11 **DR. LUCIER:** This was taken out of a review article  
12 that was prepared by Tom Clarkson a number of years ago  
13 in which these were estimates, and I think he was  
14 taking it from another source, but I think you need to  
15 keep in mind that, particularly as it relates to  
16 infants, it's an estimate, but probably one that is  
17 usable in terms of at least framing some of our  
18 questions.

19 **DR. RABINOVICH:** What is the source of that infant  
20 intake? Because you specifically stated infants. Was  
21 it formula, or it's in the environment, or is it food  
22 as the child becomes from six to twelve months of age?

1           Because --

2       **DR. LUCIER:** My guess, in a nursing infant, it would be  
3 primarily from lactational exposures. In a non-nursing  
4 infant, it would be from formula and it would be from,  
5 you know, other kinds of ubiquitous exposures. I don't  
6 -- haven't seen anything in where those exposures would  
7 have been broken down in terms of relative proportions.

8       **DR. KLEIN:** There's a statement in the European --

9       **DR. GREENBERG:** We're recording all of this, so we need  
10 to --

11       **DR. KLEIN:** Jerry Klein, Boston University.

12 I think you may have answered this question, but  
13 there's a statement from the European Agency for the  
14 Evaluation of Medicinal Products, of July 8th, that I'd  
15 be interested if you concur with. It says: "Data on  
16 methylmercury has been used in the assessment of risks  
17 associated with ethylmercury as the toxicity profile of  
18 the two compounds would appear to be similar."

19       **DR. LUCIER:** I wouldn't fully agree. I would say the  
20 limited data that's available does not justify anything  
21 else but assuming that they're similar. But I -- So I  
22 basically agree with it, but not fully.

1       **DR. GREENBERG:** We have time for one or two more  
2 questions.

3       **DR. MYERS:** Martin Myers, NVPO.

4       In these studies that are dietary intake of the mother  
5 and evaluation of the child, could you comment on the  
6 immunization practices in those communities?

7       **DR. LUCIER:** I think maybe -- Tom, did you hear the  
8 question? Tom Clarkson, who conducted the Seychelles  
9 studies, the lead investigator is here. He's asking  
10 whether or not the records that you have regarding  
11 immunization practices were kept as a part of your  
12 study. I assume they had a fairly active program in  
13 the Seychelles.

14       **DR. CLARKSON:** No. That's a very good point. I've  
15 learned a lot from this meeting, that I don't think any  
16 of the epidemiological studies, either now or before,  
17 have really taken into account the intake of mercury  
18 from vaccines. So we're going to have to look again.

19       **DR. MYERS:** So the impact we're talking about, then, is  
20 the maternal intake superimposed on the infant  
21 immunization, which I gather is quite high in that  
22 community; is that correct?

1       **DR. CLARKSON:** They have an extensive medical program  
2 there and it could be substantial. I'll have to check  
3 on that. It's an interesting point.

4 Now, bear in mind that the way we measure exposure  
5 there, and the way most of these studies measure  
6 exposure, is by biological monitoring, you see. We  
7 measure the mercury in hair or in blood, so wherever it  
8 comes from, you know, we're measuring the total  
9 exposure.

10       So although vaccines could contribute to  
11 this -- We've been assuming it's mainly coming from fish --  
12 it may contribute to this in terms of ethylmercury, we  
13 will be measuring the total mercury in blood or total  
14 mercury in hair.

15       Now, some very interesting questions come up. Only  
16 methylmercury gets into hair. Inorganic doesn't very  
17 well. So whether ethylmercury gets into hair is a very  
18 interesting question. It probably does based on the  
19 chemistry of the thing -- You know, they look very  
20 similar in their behavior -- but we have not -- we will  
21 now. We will now check the hair samples to see if  
22 there's any ethylmercury in there.

1 So this meeting's going to be useful, at least from my  
2 point of view. Thank you.

3 (LAUGHTER)

4 **DR. LUCIER:** But your -- That's a good question,  
5 Martin, and the answer is, yes, we have to think about  
6 the vaccine exposure in addition to the exposures that  
7 are already occurring.

8 **DR. GREENBERG:** Can I just ask, off the back of your  
9 notebook, do you have a rough idea, assuming that  
10 ethylmercury gets into hair as efficiently as  
11 methylmercury, what proportion of all your Seychelle  
12 data would have been vaccine-contributed, assuming that  
13 they all got their full compliment of vaccines?

14 **DR. CLARKSON:** Well, the -- Is that for me?

15 **DR. GREENBERG:** It is.

16 **DR. CLARKSON:** Bear in mind that the average level in  
17 the Seychelles in hair is about, let's say, seven parts  
18 per million, which roughly corresponds to a blood level  
19 of about 30 parts per billion. Okay. That's the  
20 average. So the calculations I showed you this  
21 morning, which were very extreme calculations assuming  
22 a very small bodyweight and assuming they got the full

1 three or four doses of vaccines, you know, the blood  
2 level might get up to 20. But you saw the -- The  
3 published figures I think were quoted from the Emory  
4 study of about 7, as I remember, 7 parts per billion.  
5 So certainly it could make a contribution. There's no  
6 doubt it could make a -- it wouldn't be an overwhelming  
7 one, but it would be a contribution.

8 **DR. GREENBERG:** Maybe I misunderstood. I got somewhere  
9 between 20 percent and 60 percent of blood level from  
10 what you just said.

11 **DR. LUCIER:** But I think you have to go back and -- I  
12 think that the age at which these assessments are being  
13 done, in the last case, in Dr. Clarkson's study, of 66  
14 months of age, and the Faroes is 84, so there's been a  
15 lot of half-lives that have elapsed since the  
16 vaccination had occurred.

17 **DR. CLARKSON:** The interesting point about -- you  
18 raised, though, about -- I mean, you're talking about,  
19 of course, post-natal exposure, now, from the vaccines  
20 -- Right?

21 **DR. GREENBERG:** Yes.

22 **DR. CLARKSON:** -- in the first six months of life.

1 Although Dr. Lucier pointed out we don't have a lot of  
2 information on this, nevertheless, both our studies in  
3 the Seychelles and in the Faroes do not find any  
4 dramatic effects of post-natal exposure levels. The  
5 Faroes is essentially cord blood correlating with  
6 adverse effects; whereas, later levels at 12 months and  
7 at 7 years, post-natal, do not seem to have much of an  
8 effect. So there's not -- There's evidence in the  
9 literature. It's really that the post-natal period is  
10 not as sensitive as the prenatal, and the numbers  
11 you're dealing with from the various agencies are  
12 coming from prenatal exposures. That's another big  
13 assumption here, that the prenatal is important to  
14 this, and it's probably not.

15 **DR. GREENBERG:** One last question.

16 **DR. DAUM:** I'm Robert Daum from the University of  
17 Chicago, and I want to follow up on something that Dr.  
18 Rabinovich was asking about.

19 I presume some babies at both of these sites are  
20 breast-fed and some babies are not breast-fed, and I  
21 guess I'm wondering about -- And this is an  
22 immunization practice question -- do very young infants

1 eat fish there? Do they eat this whale meat, blubber  
2 and things, because they certainly don't eat -- very  
3 young children don't eat fish in this country very  
4 often. So I wonder about the magnitude of the  
5 exposure, whether you expect there to be a difference  
6 given your proposed route of exposure, breast-fed  
7 versus not breast-fed.

8 **DR. LUCIER:** I wouldn't expect that they do, but I  
9 don't know that for sure. Does anyone -- Can anyone  
10 comment on that, regarding the -- particularly the  
11 Faroes study? I wouldn't expect that they'd be eating  
12 many meals of homogenized pilot whale meat.

13 **DR. GREENBERG:** I'm going to have to end this very  
14 interesting discussion now because --

15 (LAUGHTER)

16 **DR. GREENBERG:** -- I'm getting sick to my stomach.  
17 The next speaker is Dr. William Raub, who is the Deputy  
18 Assistant Secretary for Science and Policy in the  
19 Office of the Assistant Secretary for Planning and  
20 Evaluation, HHS, and the title of his talk is  
21 "Guidelines for Safe Levels of Exposure.

22 **DR. RAUB:** Thank you very much, and I appreciate the

1 opportunity to join you this afternoon. The format for  
2 the next hour, or a little bit less, is that I will  
3 make some introductory remarks around the health  
4 guidance values, and then I will be joined by a set of  
5 colleagues, including Dr. Clarkson, as a panel  
6 discussion, and they have promised to answer every  
7 question that I manage to raise.

8 We've heard repeated references or questions to the  
9 health guidance values this morning and issues around  
10 whether to use them, and if so, when and how to use  
11 them. I believe we will be able to do more to raise  
12 issues than to give sharp definitive information around  
13 some of those questions, but I thought it might be  
14 helpful to have some of the background around what  
15 these concepts are, what's the philosophy, and the  
16 generic approach to them.

17 All of these guidelines attempt to focus on a concept  
18 for which I made up a neutral name, the "Safe Daily  
19 Exposure." The emphasis is on long- term. The  
20 emphasis is generally is on very low levels of  
21 exposure. The usual units are the quantity per unit of  
22 bodyweight per unit of time. And, for example, for

1 mercury in its various forms, methylmercury, in  
2 particular, micrograms per kilogram of bodyweight per  
3 day.

4 These health guidance values are calculated  
5 individually for many different hazards, depending on  
6 the regulatory or other mission of the agency that's  
7 involved. They are calculated specifically for various  
8 primary routes of exposure, ingestion, inhalation, or  
9 dermal exposure. In general, they are projected either  
10 as a lifetime value or, more conservatively, at the  
11 very least, for some substantial indefinite period.

12 The three most common of these health guidance values  
13 are the reference dose, or RfD, of the U.S.

14 Environmental Protection Agency; the minimum of risk  
15 level, or MRL, of the Agency for Toxic Substances and  
16 Disease Registry of the Department of Health and Human  
17 Services; or the acceptable daily intake, or the ADI,  
18 employed by the Food and Drug Administration.

19 Algebraically, these are essentially the same thing.

20 They are used depending on the mission of the various  
21 agencies. They may be used as the starting point for  
22 health assessments in such situations as evaluating the

1 risks presented by a superfund site. They may be used  
2 in a formal risk assessment of a particular hazard,  
3 including all of its distributional phenomena and the  
4 like. They may be used as a starting point for  
5 developing regulatory requirements for emissions in the  
6 air or water, for assessing the toxic levels in  
7 particular situations, or, in the FDA's case, for the  
8 regulation of commercial seafood. But, again, the  
9 common factor is the notion that these are starting  
10 points for those more specific assessments and  
11 applications, and in virtually no case is the guidance  
12 value considered the last word. It's usually  
13 considered the place to begin in terms of a specific  
14 use.

15 In all of this, there is a driving desire to have  
16 science-based values to the extent possible. And in  
17 its simplest form, the algebra comes down to the notion  
18 of the safe daily exposure being a ratio of an  
19 estimated gleaned from real data, either experimental  
20 data on animals or epidemiologic observations with  
21 humans, divided by one or more uncertainty factors.  
22 And what this says is the science-based goal here

1 involves two aspects of science. One is actual data,  
2 experimental or observed, and the other are informed  
3 judgments as to the utility of that data, the  
4 limitations of it, and the ways in which it might be  
5 applied, and that's everything from the selection from  
6 the particular studies from which to fill the numerator  
7 to the judgment about the number and size and the  
8 rationale for the uncertainty factors that constitute  
9 the denominator.

10 Certain priorities obtained in general with respect to  
11 how one chooses that numerator term. Other things  
12 being equal, there's a clear preference for the -- what  
13 is called from the direct data, the "no observed  
14 adverse effect level," or the NOAEL. If there's dose  
15 response information available, and one can indeed  
16 identify the level, usually the highest level at which  
17 no adverse effect is seen, then this is often an  
18 excellent beginning for this calculation.

19 More often than not, we find ourselves faced not with  
20 the "no adverse effect" level but rather observing  
21 adverse effects in many different levels and,  
22 therefore, being forced to choose the lowest observed

1 adverse effect level. This has a bearing then on what  
2 uncertainty factor is chosen, because having seen the  
3 lowest observed one, one may have no certain  
4 information or no good basis to predict where the level  
5 of no effect actually is.

6 Another priority judgment around the selection of that  
7 numerator term is the type of information on which the  
8 experimental or observational data are based. Ideally,  
9 it's direct information on the most vulnerable human  
10 subpopulation, as we believe is the case with the  
11 Seychelles and the Faroes studies with respect to  
12 methylmercury, but sometimes one must settle for  
13 information on the general human population, not being  
14 sure at all that the most sensitive subpopulation has,  
15 in fact, been measured or that it can be discerned.  
16 Failing that, data from non-human primates are  
17 obviously desirable, and failing that, data from other  
18 mammals.

19 In the totality of these types of studies, we find  
20 ourselves, more often than not, relying on data from  
21 the bottom parts of this list, and, therefore, for all  
22 the uncertainties and complexity, as George was

1        indicating, the methylmercury discussions and debates  
2        have been a relative pleasure in that we're talking  
3        about real data on real humans, in this case, the  
4        developing fetus, and a relatively rich source of  
5        pertinent information compared to many other areas of  
6        toxicology.

7        Getting to the denominator in that element of informed  
8        judgment, uncertainties are very much tailored to the  
9        particular situation at hand. When we must extrapolate  
10       from information on humans in general to the human  
11       vulnerable subpopulation, analysts usually determine  
12       that some uncertainty factor is appropriate for that.  
13       The same is true for having the lowest observed adverse  
14       effect level, but wanting to estimate where the "no  
15       adverse effect" level might be, or at least to take  
16       account of that difference. Acute exposures  
17       extrapolated to chronic exposures, animal data used  
18       where no human information is available.

19       More often than not, the uncertainty factor chosen for  
20       any particular entry is 10, although the richer the  
21       data set the more relevant it is. Sometimes  
22       individuals doing these calculations choose a smaller

1 value, such as 3 as a half-log unit, or sometimes 1  
2 1/2.

3 If two or more uncertainty factors are employed, in my  
4 experience, more often than not, they're multiplied.

5 But, in certain circumstances, if there is some  
6 mechanistic information, one might choose to do an  
7 additive of those instead. Again, there may be no  
8 right answers with any complete determination, but  
9 informed judgments as to how best to weigh the quality  
10 and relevance of the information to the task at hand.

11 And finally, these are some, and only some, of the  
12 characteristics that affect these health guidance  
13 values. A number of my colleagues who will be speaking  
14 to you in a few minutes could give a week-long seminar  
15 on the intricacies of the assumptions and the  
16 calculations that go into these determinations. But,  
17 in general, these focus on chronic exposure, seeking  
18 that long-term, potentially lifetime level that is  
19 judged to be safe.

20 Most important, none of these are offered as a bright  
21 line between what is safe and what is unsafe. Rather,  
22 there's built in a substantial margin of safety, with

1 the realization that the number proffered is almost  
2 certain to be a safe level. Values immediately above  
3 it are most likely to be safe as well, but the higher  
4 one goes above it, the greater the risk becomes.  
5 From my point of view, they are most important the  
6 starting point for situation-specific assessments.  
7 That is, rather than giving the definitive answer to  
8 any generic set of situations, they are the values that  
9 raise the flag, they are the values that trigger  
10 curiosity or concern, and the values that cause one to  
11 look into the specifics of whatever the situation is.  
12 In this case, I believe it's been quite appropriately  
13 applied as a takeoff point, and the challenge of  
14 attempting to understand what these estimated safe  
15 daily values mean into an exposure scenario that by its  
16 very nature is episodic and where there are blips of  
17 boluses of exposure.  
18 The safe daily calculations generally assume that  
19 there's some modest excursion around that level on a  
20 day-to-day basis, but, in general, they do not assume  
21 that very large derivations on a daily basis from those  
22 are automatically included. And so, therefore, in this

1 particular situation, I think we move very quickly from  
2 using the safe daily level as an indicator for concern  
3 to some focus on, in this case, the toxicokinetics of  
4 what the nature of these particular kinds of bolus  
5 exposures might mean.

6 Last, I stress the importance of a uniformity of  
7 precaution in making these calculations across various  
8 hazards. The precautionary principle always applies in  
9 doing these calculations in that, depending on the  
10 application at hand, one wants to be sure that the  
11 level is one that one is not likely to miss a  
12 potentially problematic situation.

13 On the other hand, most risk assessors and risk  
14 managers are willing to tolerate what I'll call a false  
15 positive, as are willing to tolerate the need to do  
16 further exploration on a particular situation, only to  
17 find that it might be safe, but at least this value is  
18 set at a level that provides that degree of protection  
19 and extra caution.

20 But if each of the different hazards, say, at a  
21 superfund site, were somehow evaluated differently, if  
22 the level of precaution were extraordinarily greater or



1 Agency; Dr. Clarkson, the University of Rochester;  
2 Chris DeRosa from the Agency for Toxic Substances and  
3 Disease Registry; and Mike Bolger from the Food and  
4 Drug Administration.

5 Kate, would you like to start us off?

6 **DR. MAHAFFEY:** I'd like to do this really with some  
7 overheads, because I think it summarizes what you've  
8 heard much of this already, so we'll go through it  
9 quickly.

10 This is simply some of the things that were pointed out  
11 on the comparative knowledge about susceptibility of  
12 the young infant and the fetus. The fetal brain is  
13 considered the most sensitive. C and S development  
14 continues, of course, post-natally. We have done some  
15 PBPK modeling of lactational transfer of methylmercury,  
16 and also there are analysis data that support this  
17 showing that at the same exposure, the fetal levels are  
18 higher than the nursing infant and the nursing infant  
19 would be higher than the adult at approximately the  
20 same exposures.

21 The acceptable of mercury, whether they  
22 are -- and here we're talking about methylmercury, whether

1 it's the RfD or the MRL, are basically set for one  
2 chemical species. We don't assume a lot of  
3 contribution of either exposure or neurotoxicity from  
4 other species of that chemical or other chemicals. So  
5 it's a chemical-specific determination to get to that  
6 reference dose.

7 There were questions about the dietary exposure of  
8 infants, and I believe George had cited a review  
9 article done by Dr. Clarkson, and that was an average  
10 value, if I understood what was said, of about .05  
11 micrograms per kilogram. Our estimates based on  
12 dietary intake in this lactational transfer of  
13 methylmercury model suggests that about 7 percent of  
14 women and around 7 percent of the breast-fed infants  
15 have dietary intakes on a daily -- well, have dietary  
16 intakes in excess of the reference dose, and this is  
17 based on consumption data that's averaged over a month.

18 So it's easily a period that's long enough to be  
19 toxicologically relevant. These other numbers are a  
20 repeat of something I had shown you previously.

21 The reference dose was developed in 1995, which is  
22 prior to the publication of the data from the

1        Seychelles or the Faroes. New recommendations of our  
2        Scientific Advisory Board were that with the multiple  
3        publications coming forth, that we should sort of await  
4        the results of these before attempting to make any  
5        revisions of the reference dose. Currently, there is  
6        an NAS committee evaluating a lot of the newer data on  
7        this topic.

8        The 1995 level, though, is a benchmark dose of about 11  
9        parts per million in maternal hair. WHO had done an  
10       evaluation that suggests risk developmental deficits  
11       when maternal hair was in the 10-to-20-part-per-million  
12       range.

13       Subsequent to these evaluations, there have been  
14       publications from the Faroes and the Amazon suggesting  
15       the importance of hair mercury levels less than 10  
16       parts per million. There are also certainly the  
17       important studies from the Seychelles suggesting that  
18       higher levels of mercury exposure in that population  
19       did not produce adverse effects with the tests  
20       utilized.

21       The reference dose is considered to be a level that is  
22       associated with safety. The way it's developed, it

1 implies its exposure is safe over a long period of  
2 time. The thing that we really don't know very well is  
3 what period of time is relevant for these developmental  
4 effects, any more than we really understand what period  
5 of exposure during early infancy when infant brain  
6 development is underway would be an important exposure  
7 period for methylmercury and, certainly, by implication  
8 for the vaccine ethylmercury.

9 And just this one final point, we believe this ongoing  
10 exposure through lactation in the young infant, and  
11 then as you get some older children, 18-month-olds, 2-  
12 year-olds, may have some intake of solid food that,  
13 certainly in my experience with children, could include  
14 fish sticks, is something that you have to consider as  
15 mercury exposure. There may also be additional  
16 exposures from other mercury-containing products. So,  
17 to me, this is an example of cumulative risk of  
18 certainly exposure. The extent to which the toxicities  
19 resemble one another is something that, as Dr. Lucier  
20 has point out, we are certainly lacking data on, but  
21 there is a question of what you do with this  
22 uncertainty and the level of prudence you think it's

1 appropriate to adopt.

2 That's the extent of my comments.

3 **DR. RABINOVICH:** Can I ask a question now, or do you  
4 want to hold them to the end?

5 **DR. RAUB:** I think it might be best if we go through  
6 the panel and then do it all at once.

7 Chris DeRosa?

8 **DR. DeROSA:** I think I can dispense with the use of  
9 overheads. My comments are really things that will  
10 perhaps echo some of the things that have already been  
11 stated here, but I think they do merit further  
12 discussion.

13 From our perspective, I think it's important to view  
14 health guidance values as something other than  
15 thresholds for toxicity, and I think very often when we  
16 begin to talk about these different values that we tend  
17 to equate them with thresholds at which something is  
18 going to begin to happen, when, in point in fact, we  
19 have developed these values intentionally with the idea  
20 of building in a significant margin of safety.

21 Our value of .3 micrograms per kilogram per day, which  
22 you've seen today, we estimate is associated with the

1 margin of safety of at least tenfold, and possibly two  
2 orders of magnitude in totality. And that's fine  
3 because of the way we use the health guidance value.  
4 As Dr. Raub pointed out, we use these as a trigger or  
5 as a flag to serve as the basis for further evaluation.

6 And we carry those chemicals that are at this level,  
7 at way sites forward, for further evaluation in the  
8 broader context of biomedical and other technical  
9 judgment, what we know about demographics, what we know  
10 about other concurrent exposures, and those types of  
11 things that would serve to either elevate or diminish  
12 our concerns about exposures. But there is a bias here  
13 toward ruling out false negatives and a tolerance, as  
14 Dr. Raub pointed out, for false positives in the  
15 interest of being consistent with this precautionary  
16 principle.

17 I think that one of the things that has been mentioned  
18 here on a number of occasions is the issue of the  
19 concern about a bolus dose, and one of the things that  
20 we would possibly do in evaluating or exercising  
21 biomedical judgement as it relates to the bolus dose  
22 that is presented by vaccination or any other elevated

1 intermittent exposure would be to see how that comports  
2 with the broader database on which our health guidance  
3 value is predicated, and that would specifically refer  
4 to the peak exposure levels that we saw in the  
5 Seychelle Islands. And if we look at the mean of those  
6 peak exposures in the highest quintal of exposure in  
7 the Seychelles, we see that that mean is marginally  
8 above what we would project or what has been projected  
9 as being delivered in a series of vaccinations or three  
10 vaccinations over the period of -- a sequence of a  
11 three-vaccination -- vaccinations carried out in the  
12 first six months of life.

13 I think the other aspects that we would consider is the  
14 fact that we recognize that the developing fetus is the  
15 basis for -- the effects of the developing fetus -- on  
16 the developing fetus is the basis for our health  
17 guidance value, and that our concern here is for the  
18 neonate, and we view the neonate as sensitive to  
19 methylmercury but less sensitive than the developing  
20 fetus.

21 We would also look at the point that the average daily  
22 dose is associated with the highest quintal of exposure

1 is, again, one that is occurring throughout gestation  
2 via exposure through what the mother is ingesting, and  
3 that we know that the exposure scenario is continuing  
4 post-natally, initially through breast milk and then  
5 subsequently, as the child is weaned, through the  
6 consumption of fish, which is a very key component in  
7 several populations, including those in the Seychelles.  
8 So those are the points that I wanted to just re-  
9 emphasize or reinforce in terms of our broader  
10 discussion.

11 **DR. BOLGER:** I'm just going to make a few points that  
12 have already been made by many people before. It  
13 sounds like much of this has been discussed throughout  
14 the preceding discussions, but in terms of -- and this  
15 was what I was asked to do -- how would this -- in  
16 terms of looking at this particular issue that you're  
17 confronted with, the thimerosal issue, how would this  
18 compare in terms of the methylmercury issue that we  
19 have to deal with in terms of fish.

20 I want to pick up on several sort of key points that  
21 were made by Dr. Lucier and Dr. Raub, and in thinking  
22 about using methylmercury as a surrogate for

1 thimerosal, what are the significant areas of  
2 uncertainty that you are confronted with. All of this  
3 has already been mentioned, but I think it's -- you  
4 really have to keep this in mind, because at the end of  
5 the day you have to make a policy call and you're  
6 relying on a safety assessment.

7 So we have the -- as I see it, the very significant  
8 issue of the frequency and duration of exposure issue.

9 You have an acute intermittent type of exposure  
10 through the first year of life. Maybe somewhat after  
11 that, the time point versus the methylmercury issue,  
12 where you have generally steady state exposures that  
13 occur on a chronic basis.

14 You have the root of administration differences, the IM  
15 versus PO difference, which then leads you to the  
16 toxicokinetic differences that Dr. Lucier described in  
17 his closing remarks.

18 You also have the target organ differences between  
19 ethyl and methyl. I mean, while ethyl and methyl  
20 demonstrate remarkable, I think, similarities, there  
21 are differences in terms of specific target organs.  
22 Methylmercury, C and S, ethyl, C and S in the kidneys.

1 And then you have the dose effect differences. While  
2 this doesn't seem to be as significant an area of  
3 uncertainty as the preceding four, it is an area of  
4 uncertainty.

5 In regards to the safety assessment paradigm, and I --  
6 this has to be emphasized. I think Dr. DeRosa just  
7 emphasized this. This is a first step in an iterative  
8 process. Unfortunately, a lot of times my perception  
9 is it's perceived to be something more than that, which  
10 -- and because we -- it's described as being, well, if  
11 you exceed the safe level, you are unsafe, or I think  
12 the phrase that's commonly heard, "the population is at  
13 risk."

14 Well, that implies that the risk has gone up once  
15 you've gone over the safe level, when, in fact, the  
16 safety assessment paradigm doesn't provide you with any  
17 insights into that. I mean, the uncertainties  
18 surrounding the safe level as described in the RfD  
19 definition is tenfold. So there's really -- We don't  
20 know how the risk changes as you move about the safe  
21 level. You could risk a change not at all until you  
22 get to levels considerably above the safe level.

1 And I think in terms of the safety assessment paradigm,  
2 and I think this is the crux of the matter in my mind  
3 in terms of this particular issue, was ethylmercury,  
4 and one that we have to weigh in with in terms of  
5 methylmercury, is that it doesn't really allow you to  
6 gauge the level of effort in order to mitigate that  
7 risk.

8 In other words, you're over the safe level, then how  
9 quickly do I need to respond if I'm over the safe  
10 level? How much effort do I have to do to minimize  
11 that source of exposure? And if you try to do that  
12 within just the safety assessment paradigm, it doesn't  
13 really tell you as you move above the safe level how  
14 much risk reduction am I achieving.

15 I think -- Now, I'm not sure in terms of this  
16 particular issue with ethylmercury, because the amount  
17 of data that you have in terms of dose response with  
18 ethyl is -- my perception is fairly meager. So then  
19 you would have to use methylmercury as a surrogate, and  
20 there is a plausible way, I believe, in looking at dose  
21 response using methylmercury. That is the next step in  
22 the safety risk assessment paradigm that hasn't been

1 done.

2 I mean, in the RfD/MRL/ADI paradigm, dose response is  
3 not part of that consideration. You identify it, a  
4 particular study, you identify a particular dose level,  
5 you apply your uncertainty factors, but you are not  
6 taking into account dose response, which I think is a  
7 critical issue if you're trying to get a handle on risk  
8 above the safe level so that you can then figure out,  
9 "Well, how fast do I have to move and how much effort  
10 do I have to put into reducing this level of exposure  
11 that I'm concerned about?"

12 So those are the points I wanted to make in terms of  
13 the kinds of considerations that we have to deal with  
14 in terms of methylmercury in fish, which I think  
15 there's so much analogous to this situation.

16 **DR. RAUB:** Thank you, Mike.

17 We'll wrap up with Dr. Clarkson. As many of you heard  
18 by the repeated references this morning, much of what  
19 we know about methylmercury and its toxicity comes from  
20 the studies in Iraq and the Seychelles, and for that  
21 we're thankful to Dr. Clarkson and his colleagues.

22 **DR. CLARKSON:** Thank you, Mr. Chairman. You're more

1 than generous. We've contributed a little bit, but not  
2 that much.

3 I don't have an agenda or anything. You know, I'm not  
4 representing a government agency, but this university  
5 that lives in the tundra north, in New York State, and  
6 the only bias I have is to get as much research money  
7 as possible.

8 (LAUGHTER)

9 **DR. CLARKSON:** Naturally, that tends to make you --  
10 make things look as dangerous as possible, so that I  
11 can get more research money, but, unfortunately, in the  
12 Seychelles study we did the opposite. So we're  
13 probably going to be bankrupt before long.

14 (LAUGHTER)

15 **DR. CLARKSON:** So I don't have -- I can make comments,  
16 Mr. Chairman, about -- or we could postpone them until  
17 there's a general discussion. I don't know.

18 **DR. RAUB:** Whatever you'd like.

19 **DR. CLARKSON:** Why don't we postpone them until --

20 **DR. RAUB:** In that case, we have a substantial block of  
21 time for questions or comments. Yes?

22 **DR. RABINOVICH:** This is Gina Rabinovich, NIAID.

1 The question is generated by a comment from Dr.  
2 Mahaffey, but it probably could be commented upon by  
3 many other members of the panel.

4 In discussions leading towards this meeting, it was my  
5 understanding, and I seek clarification, that in  
6 evaluating the neurological deficits that these indeed  
7 were not overt, clinically overt, that it actually took  
8 the detailed neurocognitive evaluation to define them.

9 And you talked about clinically overt neurological  
10 deficits that maternal hair was greater than 20 parts  
11 per million.

12 We've been talking -- using that term as though it  
13 meant something. I realize I no longer know what it  
14 means. So what are we talking about, really, in terms  
15 of neurological deficits?

16 **DR. MAHAFFEY:** Well, I can tell you what we did with  
17 respect to the reference dose, and probably Dr.  
18 Clarkson can comment some, because the reference dose  
19 was based on findings from the Iraqi study. And in  
20 that, that was a poisoning episode of about six months  
21 duration. And while it's been called an acute  
22 exposure, it was certainly one that was long enough to

1 produce fetal effects.

2 Approximately two years later, two of their  
3 neurologists were in Iraq and evaluated as many of the  
4 children they could find who were born from mothers who  
5 were exposed during that epidemic, and, ultimately, I  
6 believe there were 81 maternal-child pairs who were  
7 assessed.

8 The reported paper from Marsh, et al., in 1987 talks  
9 about endpoints such as delays in walking, increased  
10 neurological scores on a standardized neurological  
11 assessment, seizures, delays in talking, and there may  
12 have been another endpoint or two in there.

13 Where the data turned difficult is that the culture in  
14 Iraq and the nomadic living conditions in these  
15 villages made it hard to find these people, as well as  
16 hard to get certain types of information from them. So  
17 there is a level of uncertainty in this data, which we  
18 readily acknowledge, but in terms of clinically  
19 significant endpoints, that's what we're speaking of.

20 **DR. RAUB:** Dr. Clarkson?

21 **DR. CLARKSON:** One of the advantages of prenatal  
22 studies versus studies in adults is you have a much

1 better recapitulation of the dose. You have to make it  
2 over a nine-month period, and so the studies that have  
3 gone on prenatally, like the Faroe studies and the  
4 Seychelles and Iraq, really are a fairly good measure  
5 of what exposure was.

6 The problem with adult studies is that you don't. The  
7 people in the fish-eating populations who are adults  
8 have been exposed all their lives, and you only have a  
9 measure going back a year or two. So it makes  
10 interpretation of a lot of the adults quite difficult.

11 So that there is a tendency, quite understandably,  
12 number one, for risk assessment to be based on prenatal  
13 exposures because of the better measure of dose, a more  
14 clear cut situation, and because the evidence seems to  
15 be the prenatal -- the developing prenatal brain is  
16 more sensitive to methylmercury. It's a big question  
17 that affects this whole debate, which is, how sensitive  
18 the situation is after birth.

19 **DR. MAHAFFEY:** If I could follow up slightly, the  
20 indications that the fetus is more sensitive than the  
21 adult, in part, comes from the Japanese epidemics, in  
22 which mothers, who themselves had very limited evidence

1 of neurological problems, gave birth to infants that  
2 had damage, clinically overt damage.

3 **DR. CLARKSON:** Yeah. The other evidence is also that  
4 in Iraq, when we examined adults -- Now, the advantage  
5 of Iraq, with all its disadvantages, is it was a sort  
6 of a short-term, six-month, or whatever, exposure, to  
7 three months to six months. So we did know, even in  
8 adults in Iraq, what the exposure was, you see, and  
9 what the maximum exposure was, which you don't know in  
10 a fish-eating population. It goes all of their lives.

11  
12 So even with adults in Iraq, you could get their  
13 maximum levels with some, you know, calculations and  
14 some assumptions, but you could come up with something  
15 that at least approximated their actual exposure, and  
16 knowing that this was a one-shot incident, there  
17 probably wasn't much exposure earlier in life.

18 Now, in that case we got, you might call, I'm an old-  
19 fashioned toxicologist -- a threshold value, say, of  
20 about 100 parts per million in hair with the adults.  
21 Whereas, with the kids, our lowest estimate was as low  
22 as 7 parts per million. Now, there's an error on that,

1 but it's the lower end of our estimate. So from a  
2 quantitative point of view, Iraq also supported the  
3 fact that the prenatal life was more --  
4 Now, the Iraqi thing, too, raised some very interesting  
5 questions about post-natal exposure. We -- Dr.  
6 Amanzaki (phonetic), who was head of pediatrics in  
7 Baghdad, examined a number of children, along with  
8 their staff, who had been exposed post-natally to  
9 mercury in milk. Of course, all feeding of infants  
10 there is from human milk until they can take solid  
11 stuff, which, of course, would be bread.  
12 And these infants, some of them were totally breast-  
13 fed, some which had -- a little older and had some of  
14 the contaminated bread. Some of these infants  
15 developed -- five of them developed blood levels of  
16 1000 parts per billion. And at least from the  
17 pediatrician's point of view, there's nothing wrong  
18 with it. Well, we weren't measuring a five-point drop  
19 in an intelligence score. But from a point of view of  
20 a pediatrician, a pretty competent, experienced  
21 pediatrician, these kids looked normal.  
22 And there was one child -- I think there was a group of

1 15 altogether. I'll have to look up the paper, but it  
2 was about 15 altogether we did. All of them were above  
3 200 in their blood levels and one of them was 1500. It  
4 was heroic. And this raises, first of all, a question  
5 about the actual sensitivity of the post-natal period.

6 I'm not sure I totally agree with my colleague, Dr.  
7 Mahaffey, that you can extrapolate from lead to  
8 mercury. She has been a lead worker after all. I  
9 think the two metals are very different in their  
10 biochemistry and in their mechanism of action, but it  
11 does raise a question about the sensitivity of this  
12 post-natal period.

13 Both the Seychelles and the Faroes, which disagree in  
14 terms of results of prenatal exposures, have not found  
15 any dramatic effects due to post-natal exposures,  
16 either in the Faroes or in the Seychelles, which also  
17 tends to give credence to the idea that the post-natal  
18 period ain't all the sensitive.

19 In fact, one of the most interesting to me of the Faroe  
20 publication, which hasn't been mentioned so far, is  
21 that they looked at children at 12 months of age and  
22 found that the higher the mercury levels in the hair of

1 these kiddies at 12 months, the better off they were.  
2 They achieved their developmental milestones more  
3 rapidly if their mercury was higher. That is kind of  
4 an interesting result.

5 The authors attributed this to a confounder. The  
6 confounder was breast-feeding, because the  
7 more -- the longer the breast-feeding period, the more  
8 mercury they got from the milk and, therefore, the  
9 higher their mercury levels were. They showed that in  
10 the study, that the length of breast-feeding actually  
11 resulted in higher mercury levels. And their  
12 conclusion was, you know, breast feeding is good for  
13 you, it's beneficial, and that was the confounder in  
14 this study. It may have a lot to do with Iraq, too,  
15 that human milk is good for you. And it raises the  
16 other issue that when we look at these numbers, whether  
17 coming from Iraq, from the Seychelles -- The media in  
18 which methylmercury is presented is very important. It  
19 might make a difference to the toxicological outcome.  
20 Certainly, the Faroes group suggested that it was the  
21 sort of protective and beneficial effects of human milk  
22 that outweighed any possible potential effects of

1 methylmercury. Something clearly was happening in Iraq  
2 to allow these very high levels.

3 Now, with thimerosal, I mean, it's a different thing  
4 altogether. It's being injected. And so you're  
5 comparing quite a different media of injection here,  
6 which might not be good news for you. I mean, you're  
7 not giving it in human milk, so you might not get the  
8 protection that you would see there.

9 **DR. RAUB:** Dr. Bolger?

10 **DR. BOLGER:** I just wanted to comment on two things.  
11 One is, bear in mind that these estimates of relative  
12 sensitivity based on the Iraqi study are fairly  
13 uncertain. I mean, we only 81 subjects in there, and,  
14 in fact, the bulk of those children's mothers had body  
15 burdens well above 50 parts per million hair levels.  
16 So you only had several subjects in the low-dose range,  
17 of course, which is the dose range of concern for  
18 methylmercury in terms of fish-eating populations.  
19 And then, in terms of the indices of development that  
20 were measured in Iraq, delayed walking and delayed  
21 talking, when Dr. Clarkson's group looked at those  
22 endpoints in the Seychelles, they did not see that kind

1 of corresponding correlation. So, bear that in mind,  
2 that there are still some significant uncertainties in  
3 terms of how you measure development and what you're  
4 looking at.

5 **DR. RAUB:** Yes? You're up again.

6 **DR. RABINOVICH:** I'm not sure if everyone is still in  
7 the nap time. I'm just trying to understand the many  
8 issues that you're raising.

9 I think I've heard it at other meetings, but perhaps it  
10 should be stated here. What do we know about breast-  
11 feeding and intake through oral and exposure to a  
12 breast-feeding infant for methylmercury, ethylmercury,  
13 whatever you found?

14 **DR. CLARKSON:** The breast milk contains a fairly  
15 proportion of inorganic mercury. People exposed to  
16 methylmercury, certainly in Iraq and in fish-eating  
17 populations, breast milk is in both the methyl and  
18 inorganic. A great deal of attention has been played  
19 to the methyl and very little to the inorganic that's  
20 coming in breast milk. This may have some reverence,  
21 this thimerosal, really, because it also breaks down to  
22 an inorganic mercury. This is not -- To the best of my

1 knowledge, it has never been looked at very much from a  
2 health risk point of view, but inorganic mercury in  
3 breast milk is probably well absorbed. In adults, the  
4 absorption of inorganic mercury averages around 7  
5 percent. There's a range, but it averages about 7.  
6 Probably in suckling infants it's much higher, of the  
7 order of maybe 50 percent. The most divalent ions are  
8 absorbed to a much higher extent in the intestines of  
9 the immature infant.

10 So one has to worry, too -- This hasn't been looked at  
11 as to how the absorption of the inorganic might have an  
12 impact, for example, on kidney function. So to the  
13 best of my knowledge, it has not been looked at in any  
14 detail, not even with methylmercury.

15 **DR. RABINOVICH:** The environmental health people, if  
16 you could summarize briefly how you think differently  
17 about organic metallic, like methyl or ethyl mercury,  
18 and inorganic mercury in terms of health impact.

19 **DR. MAHAFFEY:** Well, our understanding of this, based  
20 on Swedish data and modeling a PDPK model that was done  
21 at EPA, is that both methylmercury and inorganic  
22 mercury can enter the mother's milk, and it depends, in

1 part, on what her own exposures are. If she has  
2 comparatively high seafood intake, she can be expected  
3 to have comparatively more methylmercury in the milk.  
4 It's known, too, that dental amalgams can contribute to  
5 the inorganic mercury level in the mother's milk.

6 I was interested in Dr. Clarkson's comments about Dr.  
7 Amanzaki's work, which are found in the American  
8 Journal of Diseases of Children, Volume 130, October,  
9 1976, and I guess there must have been more infants  
10 than were written up, because this one only describes  
11 one infant who did remain well, but she was only  
12 evaluated for a short period of time, and they make  
13 specific reference to concern over what her longer-term  
14 effects might be.

15 So, I mean, you have to -- This is Amanzaki in the  
16 American Journal of Disease of Children, '76.

17 **DR. CLARKSON:** Well, we're in a better journal. We  
18 have one in the Journal of Pediatrics. Okay? So this  
19 is -- this has 15.

20 **DR. MAHAFFEY:** Okay. So there were additional ones.

21 **DR. DeROSA:** I just wanted to return to the comment  
22 about the exposure through breast milk, and there have

1       been some studies done, the Swedish study, in  
2       particular, that suggested a 50 percent distribution  
3       between the inorganic and the organic forms of mercury,  
4       that when they looked at the kids who were nursing that  
5       the relative proportion was 75 percent organic to 25  
6       percent inorganic because of the greater bio-  
7       availability, greater uptake of the organic form vis-a-  
8       vis the inorganic.

9       **DR. RAUB:** Dr. Plotkin?

10       **DR. PLOTKIN:** Well, since everybody's been  
11       extrapolating, I thought I might take a shot at it and  
12       ask the panel what they think of this. The only data  
13       we have, and, obviously, they're insufficient, are the  
14       five term infants from the Emory study who had a blood  
15       level averaging 2.3 micrograms. Assuming that they  
16       were 3 1/2 kilo infants, that means they -- and there's  
17       12.5 micrograms in hepatitis B, so they received about  
18       4 micrograms per kilo.

19       Now, at two months an infant could conceivably receive  
20       five times that. That is, 62.5 micrograms. Dr. Bolger  
21       seemed to say that there are no dose response data, but  
22       assuming what I guess is the worst case scenario, that

1 the -- you can multiply, that suggests that they would  
2 have a peak. That is, at two months, they would have a  
3 peak of 7 micrograms, assuming, of course, the factor  
4 of growth.

5 Now, is that extrapolation -- assuming that the Emory  
6 data are correct, is that way out of line, or does  
7 that, indeed, suggest that they would achieve blood  
8 levels of about 7 micrograms, which would translate, if  
9 I understood Dr. Clarkson, to about 1 or 2 parts per  
10 million in the hair?

11 **DR. CLARKSON:** I think it does. Can I show my thing  
12 again?

13 **DR. CLARKSON:** These are the data I used, which I got  
14 from Dr. Halsey, I think, by permission of the American  
15 Academy of Pediatrics, so it must be right. And  
16 obviously, those bodyweights are rather low. I used  
17 two of them: the three standard deviation one and the  
18 fifth percentile. These were the doses I was given  
19 from the vaccines; is that correct? 12.5 at birth and  
20 so on and so forth.

21 Now, if you go through the arithmetic on this, it's  
22 simple enough even for me to do it, you assume that 5

1 percent of this dose goes to the blood compartment, and  
2 that's mimicking methylmercury, I might add. And  
3 usually, distribution is complete in about three days  
4 in humans. Then you assume that the volume of the  
5 blood compartment -- Dr. Halsey, correct me if I'm  
6 wrong. You said 8 1/2 percent of the bodyweight,  
7 correct?

8 **DR. HALSEY:** At birth.

9 **DR. CLARKSON:** At birth, yeah. Well, I took it for six  
10 months, as well. Not being a pediatrician, I just did.

11 So if you do that -- Because I felt they're only  
12 numbers, you know, you can do the arithmetic better  
13 than I can -- you come up with blood levels shown on  
14 that last column -- Can you read that? -- of -- Well,  
15 not on that. That's the dose. Now, the blood levels  
16 you get are on the next slide, which I showed you this  
17 morning, and you can see that it's a small dose at  
18 birth. The yellow one is the smallest bodyweight, of  
19 course, the three standard deviation one. If you can  
20 read the white one, it's the fifth percentile. You can  
21 see that after the first vaccination, background levels  
22 in blood are about 1 part per billion, depending on

1 fish consumption and all that. Generally speaking,  
2 they're down there. You get a modest increase to less  
3 than five.

4 And then this decline here is simply due to the  
5 increase in bodyweight. I'm making that key assumption  
6 that there's no excretion whatsoever of mercury during  
7 this period, and that assumption comes only from animal  
8 experiments. We think we know the mechanism of that,  
9 but we don't -- and it probably should apply to humans,  
10 but there's no observations made yet on humans.

11 And I think this -- this discussion of vaccines might  
12 help us solve this problem, might be able to get some  
13 samples. Don't give me too many fecal samples at once,  
14 but we want to be able to get some samples that might  
15 solve this problem.

16 And then when you give the larger dose, the 62.5,  
17 obviously, there's a rather sharp increase, again a  
18 decline due to growth, and so forth. You can see this  
19 sort of pattern will eventually get you up into the  
20 20s.

21 Now, the regulatory guidelines are roughly for EPA  
22 around 5, 4 or 5. I think FDA is around 20. It's the

1 classic one we've had for ages and ages. WHO, as well,  
2 is around 20, about here. So that we just edge up and  
3 sort of go between the various guidelines on that.

4 It's a matter of what arithmetic you want to do, what  
5 assumptions you want to make about the bodyweight of  
6 the child, and how frequently the vaccines are given,  
7 and what's the mercury in the vaccines.

8 And my view is that it's the maximum level that  
9 determines the damage. Methylmercury is an  
10 irreversible poison. It knocks out the brain cells.  
11 So probably, it's not so much the length of exposure,  
12 it's the peak exposure that's really going to do the  
13 total damage. The Iraq dose response that the EPA used  
14 in their risk assessment was based on peak levels, not  
15 average levels, but peak levels. And so in this sense,  
16 it's the peak levels here I would imagine that are  
17 probably important to worry about.

18 And this is obviously a worst-case scenario. These are  
19 the lowest possible bodyweights. And I heard this  
20 morning that you're not even supposed to give a vaccine  
21 to an infant at 1.8 kilograms, and this is 1.8  
22 kilograms here. Okay? Thanks.

1       **DR. RAUB:** We just have a few minutes. There's one  
2 hand in back and then a couple down front here. We  
3 probably have time for about two or three more  
4 questions.

5 The gentleman in the back?

6       **DR. BERNIER:** My name is Roger Bernier from the  
7 National Immunization Program at CDC.

8 I wonder if we could get some more discussion about the  
9 application of these standards, because I think one of  
10 the things that characterized the policy-making around  
11 this episode was, I think, the perception or the  
12 interpretation of these guidelines as in some ways  
13 bright lines where there, in fact, was a violation of  
14 safe levels. And the insights that I'm getting from  
15 hearing you talk about these is very interesting  
16 because you're talking about these guidelines as  
17 starting points, as screening levels that you would  
18 then begin to investigate further. I guess it suggests  
19 to me that there's an art to the application of these  
20 guidelines.

21 And I wonder if you have ideas about, or from past  
22 experience, a protocol or a checklist for once you have

1 hit this screening level and you are now beginning your  
2 further investigation, what are the things to do. I  
3 mean, from other situations where you have experienced  
4 violations or things have occurred in excess, is there  
5 guidance that you can give in this art of applying  
6 these standards so that we can then judge what we are  
7 doing in the vaccine area and how we are doing as  
8 appliers of these standards?

9 **DR. MAHAFFEY:** If I could offer one comment. One of  
10 our concerns with our estimates for reference dose and  
11 mercury exposure is over what time period of both  
12 exposure and, in the case of methylmercury,  
13 developmental period these exposures are appropriate  
14 for.

15 When we did the report to Congress, there was a lot of  
16 back-and-forth discussion over what time period of  
17 exposure we should average mercury intake from fish.  
18 We had some daily exposures in there. We had monthly  
19 exposures in there, too. Certainly, the day-to-day  
20 variability in fish intake will produce a much higher  
21 range of exposure if you look at a one-day kind of  
22 intake.

1 At that point, we looked at 30-day intakes.

2 In listening to the experimental animal panel talk  
3 about the importance of an intermittent high-dose  
4 exposure on C and S development, at least in animals, I  
5 personally began to wonder if our 30-month period was  
6 too long. I don't know what the appropriate period  
7 really is, but it has been the topic of a lot of  
8 discussion.

9 The reference doses are intended to be a level that's  
10 thought to be safe over a very long period of exposure,  
11 and clearly what that relevant period is can be, in  
12 part, determined by the what the endpoint is you're  
13 trying to look at. If you're looking at  
14 carcinogenicity, clearly a longtime period of exposure  
15 is the period of greatest interest. With  
16 methylmercury, we know that there are developmental  
17 windows of importance.

18 I think with this, as others have pointed out, this  
19 peak exposure that happens is something that is  
20 fundamentally quite different from the usual  
21 application of reference doses, and I would think the  
22 kinetic information has got to be very important here

1 because it may suggest that the risk is higher than  
2 what might be assumed from just applying the reference  
3 doses, or the MRL.

4 On the other hand, additional kinetic data may show  
5 that ethylmercury is a sufficiently different compound  
6 in its metabolism that the RfD, or MRL for  
7 methylmercury, may not be that relevant, but, in the  
8 interim, risk managers will have to make some  
9 decisions.

10 **DR. GREENBERG:** I think this has been a great  
11 discussion, but we should take a break now. You can  
12 continue this discussion in the hallways, and we'll be  
13 back here at 3:30 for the last session.

14 (RECESS FROM 3:00 P.M. TO 3:34 P.M.)

15 (END VOLUME I - DAY ONE)

16 **SEE VOLUME II - DAY ONE)**

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C E R T I F I C A T E

G E O R G I A )

FULTON COUNTY )

I, Pamela T. Lennard, being a Certified Court Reporter in and for the State of Georgia, do hereby certify that the foregoing, consisting of pages 1 through 221 (VOLUME I - DAY ONE), inclusive, was reduced to typewriting by me personally or under my supervision and is a true, complete, and correct transcript of the aforesaid proceedings reported by me.

I further certify that I am not related to, employed by, or attorney or counsel for any parties, attorneys, or counsel involved herein; nor am I financially interested in this matter.

WITNESS MY HAND AND OFFICIAL SEAL, this 5th day of September, 1999.

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Pamela T. Lennard, CCR-CVR  
CCR No. B-1797

[SEAL]