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PUBLIC HEALTH SERVICE
CENTERS FOR DISEASE CONTROL AND PREVENTION**

convenes

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

**DAY ONE - VOLUME I
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P R O C E E D I N G S

8:32 A.M.

1
2
3 DR. MYERS: Good morning, and welcome to the
4 National Vaccine Advisory Committee Sponsored Workshop
5 on Thimerosal in Vaccines. By starting exactly on
6 time, I hope we'll stay on time, which may be the
7 challenge for the -- for the moderators.

8 I'm Martin Myers. I'm the Deputy Director of the
9 National Vaccine Program Office, and I appreciate the
10 willingness of so many people to participate in the
11 middle of the summer and on such short notice on this
12 very important and timely topic.

13 I have a number of housekeeping and a number of
14 specific things, from a format point of view, to say.
15 The first and most important thing, and someone told me
16 this morning that the only real important job of the
17 person who welcomes, is to say that the restrooms are
18 outside by the elevators. There is a cafeteria
19 downstairs, which is very small. We'll use that for
20 our breaks. We'd suggest that for the lunch hour that
21 people go to the Natcher Auditorium, which is out the

1 front door and the building straight ahead of you,
2 across the street, which has a much larger cafeteria
3 than is in this building.

4 Thimerosal has been used as an additive to a
5 number of biologics since the 1930s, including some
6 vaccines routinely recommended for use in young
7 children. Because of multiple doses of vaccine, it is
8 possible that some children could be exposed to a
9 cumulative level of mercury that exceeds guidelines for
10 methylmercury.

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

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

20 It's very -- It's important to discuss, as we
21 discuss these issues, to balance these with the very

1 real risks of disease resurgence if we have a reduction
2 in vaccine utilization or a loss of confidence in
3 vaccines.

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

14 The workshop is convened specifically for the
15 exchange of information. It is not a policy meeting
16 nor is it designed to provide advice.

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

1 years with thimerosal.

2 Then we're going to talk about organomercurials,
3 both thimerosal as an organomercurial-containing
4 additive as well as organomercurials in general.

5 We're going to end the afternoon talking about
6 potential disease impact of the diseases that are --
7 the vaccines that would be primarily affected during a
8 transition to a reduced thimerosal vaccine supply.

9 Tomorrow we're going to talk about the transition
10 to a greater supply of thimerosal-free vaccines in
11 reduced thimerosal-containing vaccines. We're going to
12 talk about issues that relate to the manufacturer and
13 regulatory activities, the European initiative, and
14 then we're going to talk about the transitional vaccine
15 options, the flexibility within the recommended
16 schedule.

17 At that time, we're going to -- we have a number
18 of groups and individuals who would like to participate
19 by giving their perspectives on these options. We have
20 allowed time in that session for others who would like
21 to give their perspective on this, as well. We didn't

1 know how much time to allow. We have limited time. We
2 have a very full agenda for the next couple of days.
3 So if there are individuals or groups that would like
4 to give a perspective on this, if they'd put together a
5 one- or two-sentence summary, we've asked Dr. Modlin,
6 who is going to be our moderator tomorrow, to triage
7 these and work that last minute changes on the agenda.

8 And then, finally, many of us feel that
9 the -- one of the most important parts of this meeting
10 will occur at the end, which is a discussion of
11 knowledge gaps that exist.

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

15 To use the microphones, the individual microphones at
16 your seats -- I've got to read this here, and it's
17 tough with bifocals -- you need to depress the "Request
18 to Talk" button, and red and green lights will come on,
19 and that means that the microphone is on, and then you
20 depress it again to turn it off, and both lights will
21 go off. We'll ask our moderators to triage the

1 questions and also to keep us focused and on time.

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

7 Dr. Harry Greenberg will be our moderator today.
8 Dr. Greenberg is the Chair of the VERPAC. Dr. John
9 Modlin will be our moderator tomorrow, and he is the
10 Chair of the ACIP. Again, they're going to make every
11 effort to keep us on time.

12 We are going to develop proceedings from this
13 meeting. Therefore, even though everybody knows you in
14 the room, if that's the case, please tell us who you
15 are and your affiliation, so our transcriber will be
16 able to put that together.

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

19 **DR. KLEIN:** Thank you, Dr. Myers. It's a
20 privilege to be a participant in this very -- what I
21 anticipate will be a very informative experience for

1 all of us. I think we start out with a relatively
2 limited base of information about organomercurials and,
3 particularly, about concerns for these products in
4 vaccines.

5 The specific issue of thimerosal is one that is --
6 has history of about sixty years. Its use as
7 preservative in biologics and pharmacologic
8 preparations goes back to the 1930s, and it is present,
9 or has been present, not only in vaccines, but in
10 various cosmetics, contact lens solutions. So its use
11 as a preservative goes beyond the specific area of
12 vaccines.

13 Thimerosal is an ethylmercury salt, and it's
14 important to keep the distinction about the disasters
15 that have occurred with mercury with which we are
16 familiar from the paucity of information about any
17 harmful effects of ethylmercury, but we'll hear more
18 about that.

19 Thimerosal is present in some but not all
20 vaccines. Most of the viral vaccines do not have
21 thimerosal. Both the oral and inactivated polio

1 vaccines do not. Measles/mumps/rubella does not.
2 Varicella vaccine does not. Rotavirus, hepatitis A,
3 and Lyme disease vaccines all do not have preservatives.
4 They don't have thimerosal.

5 Thimerosal is present in some but not all DTP and
6 DTaP preparations. Some of the hepatitis immune -- I'm
7 sorry -- amphophilous influenza B, polysaccharide
8 conjugate vaccine, the benignococcal and pneumococcal
9 polysaccharide vaccines, as well as hepatitis B. And
10 there will be more discussion about the focus of
11 changes for hepatitis B vaccine.

12 This product is antibacterial and prevents, as
13 well as may treat, infectious agents that are present
14 in these various products. The antibacterial activity
15 is related to release of ethylmercury after spontaneous
16 or enzymatic breakdown of thimerosal into ethylmercury
17 and thiosalicylate. It is bactericidal at acidic pH.
18 It is bacteriostatic and fungistatic at alkaline or
19 neutral pH.

20 The most frequent adverse events that have been
21 identified with thimerosal are those of a

1 hypersensitivity reaction, papular or vesicular
2 disruptions. Some of the solutions for contact lenses
3 have caused eye irritations.

4 It is methyl, not ethyl, toxicity that has been
5 associated with the well-known events in Minamata,
6 Japan, resulting from the contamination of fishing
7 waters in the area and the severe consequences for
8 people in that area.

9 Use of methylmercury has been as a fungicide, and
10 the mistaken use in preparation of homemade bread
11 rather than grain for planting in Iraq led to many --
12 severe morbidity and mortality.

13 In contrast then, thimerosal is ethylmercury; and
14 to underline, there is no evidence of harm from the
15 amounts of mercury administered to infants and children
16 in vaccines.

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

19 One, the use of preservatives in vaccines, are
20 they necessary? Are they necessary for specific
21 products? Are there are substitutes that can be made

1 if they are necessary for the thimerosal that is now
2 used?

3 Two, we'll talk specifically about mercury and the
4 pharmacokinetics and toxicology in animals as well as
5 some human data.

6 Three, the impact, and there will be considerable
7 discussion later today on any issues that arise that
8 may limit public confidence in vaccines and alter our
9 current success in immunization program.

10 Four, what are the current plans to reduce or
11 eliminate thimerosal in vaccines?

12 Five, the pragmatic issues about what to do during
13 the transition from the current roster of vaccines that
14 do contain thimerosal to a thimerosal-free vaccine,
15 period.

16 And then finally, a review of appropriate
17 priorities for research in these areas.

18 So I anticipate an educational experience for all
19 of us.

20 To begin this morning's program, I'd like to
21 introduce the moderator for the morning session, Dr.

1 Harry Greenberg, who is Senior Associate Dean for
2 Research at Stanford University and Chief of Staff of
3 Research at the Palo Alto VA.

4 Dr. Greenberg.

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

13 The purpose, I think Dr. Myers really hit the nail
14 on the head when he said the main purpose of this
15 meeting is to get all of us on the same page as far as
16 our database as to what the issues are here, and I look
17 forward to a very, very informative meeting.

18 We're ahead of time, and maybe we'll be able to
19 keep ahead of time during the meeting, but if, by
20 chance, that doesn't occur, like it never does, I may
21 have to cut off some of you who I am sure have the most

1 important question to ask. It is nothing personal, but
2 I will use my prerogative to keep the meeting on time.

3 And so, trying to keep it -- keep on schedule, I'd
4 like to introduce the first speaker, who is Dr. William
5 Egan, Acting Director, Office of Vaccine Research and
6 Review at CBER, FDA, and he's going to start off that
7 first session that we're talking about: Where Are We
8 Now: A Review of the Data -- Thimerosal in Vaccines.
9 His perspective is from the FDA.

10 Bill? First, I'm starting his time. Instruction
11 is on your time.

12 (LAUGHTER)

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

17 Let me begin by relating one incident that's
18 described in Sir Graham Wilson's classic book, "The
19 Hazards of Immunization." It goes:

20 "In January, 1928, in the early stages of an
21 immunization campaign against diphtheria, Dr. Ewing

1 George Thomson, Medical Officer of Health at Bundaburg,
2 in Australia, began the injection of children with
3 toxin-antitoxin mixture. The material was taken from
4 an India rubber-capped bottle containing 10 mLs of the
5 toxin-antitoxin mixture. On the 17th, 20th, 21st, and
6 24th of January, Dr. Thomson injected subcutaneously a
7 total of twenty-one children without ill effect.

8 On the 27th, a further twenty-one children were
9 injected. Of these children, eleven died on the 28th
10 and one on the 29th."

11 The death of these twelve children was
12 investigated by the Royal Commission, and the final
13 sentence in the summary of their findings reads as
14 following:

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

19 As Sir Graham Wilson also notes in his book, staph
20 toxin was very likely also present in the bottle, thus
21 accounting for the rapid deaths of the children.

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

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

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

18 However, from these disasters, these and similar
19 disasters, have arisen the regulations that require
20 preservatives in multi-dose, multi-entry containers of
21 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
13 multi-dose containers shall contain a preservative,
14 except that a preservative need not be added to Yellow
15 Fever Vaccine; Polio-Virus Vaccine, live oral; viral
16 vaccine labeled for use with the jet injector; dried
17 vaccines when the accompanying diluent contains a
18 preservative; or to an allergenic product in fifty
19 percent or more in volume of glycerine."

20 The CFR also requires that a preservative that is
21 used shall be sufficiently nontoxic so that the amount

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

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

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

1 Division of Product Quality Control, had the following
2 comment:

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

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

1 Let me show some data that was presented by
2 Koerner and Kindt from the (inaudible) in Germany at
3 this symposium twenty-five years ago. Well, this is
4 filling data, so number of lots that were filled and
5 the percentage of non-sterile filling lots. And with
6 no preservatives in ampules, 5.6 percent of the lots
7 were found to be non-sterile. This is using the test
8 that's in the CFR. For multi-dose containers, somewhat
9 better, 2.2 percent. And even when preservatives were
10 used, if we look at the ampules, the number of lots
11 that were rejected went from 5.6 to 4.4 with phenol, to
12 2.1 with an organomercurial. In the multi-dose
13 containers, it went from 2.2 down to 0.3 with phenol
14 and 0.8 with the organomercurial.

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

21 And even in the -- with no preservatives, with the

1 multi-dose containers with some residual formaldehyde,
2 it was the same as no preservative. Formaldehyde does
3 nothing.

4 The reason I show these data is simply to point
5 out that even with the preservatives, there was still a
6 number of lots that were rejected because of issues of
7 stability.

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

14 However, I point this out simply to say that the
15 numbers will not be zero and the risk of no
16 preservative will be slightly greater than with the
17 preservative. No matter how small they are, the
18 numbers are not zero. There may be some discussion
19 later on this point.

20 Now, I've spoken for the past nearly ten -- five,
21 ten minutes about preservatives, but have yet to say

1 what a preservative is and what precisely we expect a
2 preservative to do. If I may come back and quote Dr.
3 Seligman again, he mentioned that the sole reason for
4 adding a preservative is to protect the recipient.
5 Thus, a preservative must be able to protect the
6 recipient from the consequences of inadvertent
7 microbial contamination while at the same time being
8 nontoxic to the recipient and not denaturing the
9 product.

10 Sodium azide is a good preservative, but it's use
11 in (inaudible) would not be allowed because of
12 toxicity. Thimerosal is a good preservative, but not
13 for IPV. It inactivates the vaccine. Hence, we have
14 the regulations that I showed before, that a
15 preservative must be nontoxic and must not denature the
16 particular substance.

17 But what needs a preservative to do? Obviously,
18 as I've said, a preservative must prevent the
19 consequences of inadvertent contamination by
20 microorganisms introduced during use of the product.

21 However, does this mean that a preservative must

1 be bactericidal or fungicidal, or is it sufficient that
2 the preservative assure microbial stasis? And whether
3 a preservative should be cidal or simply ensure stasis,
4 we need to ask as well, against what organisms, at what
5 levels, and if a preservative must be cidal, how
6 rapidly. These issues are not addressed in the Code of
7 Federal Regulations.

8 Now, under proper conditions of storage, usually
9 refrigerated, and with good medical practice, the
10 extent of potential inadvertent contamination should be
11 minimal. The number of -- The number of the types of
12 potentially contaminating organisms is quite large, and
13 there are long lists in various texts on preservative
14 and stabilities. And there could be and there has been
15 considerable argument regarding which organisms a
16 preservative should be able to exclude. However, if we
17 look at past examples, past tragedies, that list would
18 certainly include the staphylococci and streptococci.

19 Now, preservatives are also discussed in the
20 United States Pharmacopeia, and the USP regards
21 antimicrobial preservatives as substances added to

1 dosage forms to protect them from microbial
2 contamination. They are used mainly in multi-dose
3 containers to inhibit the growth of microorganisms that
4 may be introduced inadvertently during or subsequent to
5 the manufacturing process.

6 The USP further states that any antimicrobial
7 agent may exhibit the protective properties of a
8 preservative. However, all useful antimicrobial agents
9 are toxic substances. For maximum protection to the
10 consumer, the concentration of the preservative should
11 be considerably below the concentrations of the
12 preservative that may be toxic to human beings.

13 These discussions of a preservative that are in
14 the USP are thus quite similar to those in the CFR.
15 The USP, however, does provide a functional definition
16 of preservative, whereas the CFR does not.

17 I should add also that the USP tests a
18 preservative only in the original unopened container in
19 which the product was distributed by the manufacturer.

20 So it's not a preservative, per se, as an entity, but
21 only that entity in a specific product.

1 Now, an ample number of examples may be found in
2 literature wherein a substance at a particular
3 concentration functions as a preservative, per the USP
4 definition, for one biological product but fails in
5 another. For example, a preservative at a -- a
6 material at a particular concentration may be a good
7 preservative for a vaccine, but in a blood product or
8 in serum does not function -- does not function, does
9 not meet the USP requirements.

10 Now, let me outline briefly the USP definition of
11 "preservative." It's a functional definition wherein a
12 specified amount of the product is challenged with a
13 known quantity -- Actually, 0.1 milliliters of
14 approximately 10^5 to 10^6 per ml of the following
15 organisms, or spores: candida albicans, aspergillus
16 niger, escherichia coli, staphylococcus aureus, and
17 pseudomonas aeruginosa, and it specifies the strains
18 from the American-type culture collection.

19 The test sample is incubated at 20 to 25 degrees,
20 and the number of viable organisms determined on days
21 7, 14, 21, and 28. And a preservative is then

1 acceptable if bacteria are reduced to less than 0.1
2 percent of the challenge dose by day 14; yeast and mold
3 remain at or below the initial inoculum on day 14, and
4 the number of organisms -- This should be on day 28 --
5 are the same or below that on the day 14 level.

6 Now, for bacteria, the USP definition is a
7 bactericidal one. For yeast and mold, the definition
8 is one of stasis. Although the choice of challenge
9 organisms might be argued, most people would agree that
10 the USP challenge assay is quite stringent in that the
11 challenge doses are much greater than might ordinarily
12 be expected to occur through inadvertent contamination
13 during use. Thus, a preservative, as defined by the
14 USP, provides a large margin of safety.

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

18 The preservative that is in the CFR is a preservative
19 as defined in the USP.

20 The simple answer to this question is no. A
21 material that does not meet the USP requirements may

1 still be deemed by CBER to satisfy the CFR requirements
2 for a preservative. Although a material satisfying the
3 USP definition will certainly be acceptable as a
4 preservative, other definitions are possible.

5 However, if a different set of requirements are to
6 be met -- different organisms, different
7 concentrations, different times to kill, et
8 cetera -- then the rationale for their use must be
9 presented to CBER for approval in the products.

10 Now, we're at the workshop today to discuss
11 thimerosal and its reduction and removal -- well,
12 removal from existing products. This will entail
13 switching to single-dose vials without preservatives or
14 using single-dose and multi-dose vials with different
15 preservatives. Such changes may constitute a change in
16 formulation of the product. Dr. Baylor, in his talk
17 tomorrow, will discuss how CBER will handle these
18 product formulation changes from a regulatory point of
19 view.

20 A little later in this talk -- in this session,
21 Dr. Ball from FDA will be discussing the vaccines that

1 contain thimerosal, the content of thimerosal in those
2 vaccines, and the guidelines that are now existing
3 regarding mercury intake, and I believe that Dr.
4 Plotkin will be following me and presenting some data
5 on alternative preservatives.

6 Okay. Nineteen minutes, Harry. You got one extra
7 minute.

8 DR. GREENBERG: Thank you, Bill. Stay up here
9 because we have some time for some questions. I'd like
10 to thank you for an excellent talk.

11 Can I ask the first question? I assume that
12 thimerosal or thimerosal --

13 DR. EGAN: Actually, one's used -- one is the term
14 used in Europe, the other is the term used in the U.S..
15 They're the same chemical.

16 DR. GREENBERG: Good.

17 DR. EGAN: Next question.

18 (LAUGHTER)

19 DR. GREENBERG: I assume that that fits under the
20 USP definition.

21 DR. EGAN: Yes.

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

5 DR. HALSEY: Two questions, one -- the first one
6 is, does that USP --

7 DR. GREENBERG: Could you stand up and identify
8 yourself to the audience?

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

10 DR. GREENBERG: Then you can sit down.

11 (LAUGHTER)

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

13 DR. HALSEY: All right. Two questions. The first
14 one is: Does the USP test, the pharmacopeia test,
15 require the product to be used -- that preservative to
16 be tested in the final product, and is this being --

17 DR. EGAN: Yes.

18 DR. HALSEY: -- because of the -- If you might
19 address the issue of the contamination of DTP with
20 Group A strep, and Group A strep is not one of the
21 organisms which you mentioned back there, but the basis

1 for why that doesn't work as perfectly as we would like
2 to, because there are multiple reports of clusters of
3 those cases, and I have always assumed it was because
4 of the particular matter that was in DTP that may have
5 played a role in helping protect it.

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

16 **DR. EGAN:** Okay. Let me try the first question
17 first. That related to the USP definition about
18 whether it corresponds to the preservative in the
19 material, and the answer to that question is yes. So,
20 in other words, they take the final dosage formulation
21 and then it's challenged with those five -- those five

1 organisms.

2 Your second question was --

3 DR. GREENBERG: Bill, I --

4 DR. EGAN: Yes?

5 DR. GREENBERG: Neal, it seems to me that your
6 second question is the purpose of this meeting. So
7 rather than, in the first speaker, trying to -- I think
8 maybe you'd be wise to ask that question at the end of
9 the meeting.

10 Now, any other questions?

11 DR. McINNUS: Pamela McInnus, NIAID. I'd like
12 some clarification following this first talk: Are we
13 moving forward with this workshop on the basis that
14 available data do support the decision to reduce and
15 eliminate thimerosal? Is that up for discussion at
16 all, or is that decision made and is nonretractable?

17 DR. EGAN: Okay --

18 (LAUGHTER)

19 DR. EGAN: Well, let me speak for myself
20 personally, and I believe that we -- you know, we,
21 i.e., FDA, have made that decision to -- whenever

1 possible, to eliminate thimerosal from products. We
2 have asked manufacturers and sponsors in the
3 development of their products to develop them without
4 thimerosal; and if they're not able to do that, to
5 specifically explain why.

6 So the use of thimerosal as a preservative is no
7 long the default option.

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

14 **DR. GREENBERG:** Pam, I would like to say, also I
15 think your question, at least for me, who is less well-
16 informed than many of you, that part of the purpose of
17 this meeting is to get a database in front of all of us
18 at the same time and then potentially to re-evaluate
19 decisions that were made, but at least to have a very
20 broad and deepening airing of available information so
21 that your question can be answered in a scientific way.

1 Any other questions? In the back?

2 DR. CORDERI: José Corderi, CDC. Bill, what
3 preservatives are now available, other than thimerosal,
4 that would meet the USP definition for preservative?

5 DR. EGAN: For the common childhood vaccines, the
6 only one that I'm aware of that -- in the product
7 formulations that is used is 2-phenoxyethanol.

8 DR. CORDERI: Any others?

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

15 DR. GREENBERG: Other questions?

16 (NO RESPONSE WAS HEARD)

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

20 The next speaker is Dr. Stanley Plotkin, who is
21 now the Medical and Scientific Advisor to Pasteur

1 Mérioux Connaught, and he is going to be talking to us
2 about preservatives, the manufacturer's perspective.

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

10 Indeed, after I am done speaking, manufacturers in
11 general, and Pasteur Mérioux Connaught, in particular,
12 may choose to disavow what I have to say.

13 (LAUGHTER)

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

21 Subsequently, there was an urgent meeting called

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

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

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

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

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

21 Thus, three changes had taken place with respect

1 to the use of thimerosal. First, the perception of
2 danger, experience with methylmercury exposures, and
3 increasing environmental concerns led the EPA to issue
4 strict guidelines with respect to mercury exposure.
5 These guidelines were designed to provide a margin of
6 safety based on the available data concerning toxicity
7 of 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
13 disagreement between agencies and where industry may
14 have been following a guideline that could be abandoned
15 or altered.

16 It is important to understand, as I learned, what
17 is meant by a guideline. The statement on this slide
18 is 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

1 levels, and these were a blood level of 11 -- I'm sorry
2 -- of 44 micrograms per liter of blood; hair
3 concentration you can read; and then an uncertainty
4 factor of 10 was used to derive the acceptable dose,
5 which was thought to be safe. It was stressed that
6 this reference dose is likely to be without appreciable
7 risk of deleterious effects during a lifetime.
8 Exceedence (sic) does not mean that risk will be
9 present.

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

16 The second change is the increasing number of
17 licensed vaccines recommended for infants. While some
18 of us perceive that as a good thing, the concern is
19 that this development may be associated with an
20 accompanying increase and exposure to thimerosal. I
21 would point out, however, that thimerosal containing

1 DTaPs have the same concentration of thimerosal as
2 whole cell DPTs, so there was no change there.

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

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

18 However, and I will -- Well, however, routine
19 neonatal vaccination of premature infants was never
20 recommended. The Redbook recommendation here is that
21 infants be allowed to reach two kilograms of weight

1 before being vaccinated against hepatitis B, unless
2 their mothers are hepatitis B carriers.

3 Let me now touch briefly on the data that formed
4 the basis of concern regarding thimerosal. I must
5 start with a disclaimer that I am certainly not a
6 toxicologist and would never presume to give an opinion
7 concerning acceptable levels of mercury. However, I do
8 have a fair amount of experience in evaluating
9 scientific evidence.

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

17 Second, with respect to methylmercury, it appears
18 that there are only two large epidemiologic studies
19 concerning methylmercury exposure, both occurring after
20 eating fish, and they are in disagreement. The study
21 in the Seychelles was reassuring in that chronic

1 exposure of mothers to more mercury than is present in
2 vaccines was not followed by abnormalities in children.

3 Whereas, in the Faroe Islands, perhaps because of
4 binge eating of pilot whales or because of concomitant
5 ingestion of PCBs, subtle effects in learning
6 correlated with blood levels of mercury. The blood
7 levels, just to remind you, were on the order of 23
8 micrograms per liter, with an interquartile range of
9 13.4 -- It's a mistake on the slide -- to 41. The mean
10 was 22, as I said, and 75 percent of infants had cord
11 blood levels over 13 micrograms. Also noteworthy is,
12 it appeared to me, that the hair mercury levels in the
13 mothers were similar to those in the Seychelle study.

14 So no data have been produced to suggest that
15 vaccinated children have suffered from thimerosal
16 toxicity aside from the allergic reactions already
17 mentioned.

18 Admittedly, the effects found in the Faroe Islands
19 exposure to methylmercury are subtle and might be
20 missed by passive reporting. At least, however, one
21 epidemiologic study done in the United Kingdom

1 comparing scholastic achievement in pertussis-
2 vaccinated children versus unvaccinated children, as
3 quoted in the IOM report on adverse reactions to
4 pertussis vaccine, show that vaccinated children were
5 doing better in school, an effect that was attributed
6 to their parents being smarter.

7 (LAUGHTER)

8 **DR. PLOTKIN:** I mentioned -- It's true. I
9 mentioned previously the study reported in abstract for
10 memory in which blood levels of mercury were measured
11 before and after neonatal hepatitis B vaccination in
12 five full-term infants and fifteen premature infants.
13 The post-vaccination blood levels averaged 7 micrograms
14 in very low birth weight infants, compared to 2 to 3
15 micrograms in full-term infants. The mean gestational
16 age of the premature infants is given in the abstract
17 as 25 weeks. This would mean the infants were mostly
18 below a thousand grams in weight and should not have
19 received the vaccine in the first place.

20 However that may be, a few percent of those
21 prematures had peak blood levels in the range of cord

1 bloods associated with learning defects in the Faroe
2 Islands study. No pharmacokinetics follow-up was done,
3 but the Emory data would seem to reinforce the earlier
4 recommendation, not to vaccinate premature infants of
5 very low birth weight.

6 Plus, there seems to be a paucity of data in the
7 literature to show that infants receiving ethylmercury
8 accumulate mercury in excess of infants who are simply
9 exposed to mercury in the environment.

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

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

20 Each preservative must pass tests prescribed by
21 the U.S. or European Pharmacopeia, as Bill Egan has

1 already stressed. And he already pointed out that,
2 although in real life situations, the preservative
3 simply has to keep organisms from growing. When tested
4 for regulatory approval they must show an ability to
5 decrease the number of viable bacteria.

6 Now, I just wanted to show a few slides on
7 comparisons. Here we see a study that was done in the
8 U.S. in 1981 in which we see that thimerosal actually
9 in this test failed against staph aureus, failed
10 against the USP criterion. 2-phenoxyethanol also
11 failed against e. coli. In this particular test,
12 phenol was the best.

13 Two more recent studies done in Europe gave the
14 following results. On these slides, "A" means
15 fulfilling the Pharmacopeia's requirement, "B" means a
16 slower killing effect than is stated in the
17 Pharmacopeia, and "C" means stasis. "Inc" is
18 incomplete.

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

1 the same.

2 And another comparison done by another
3 manufacturer again shows thimerosal to be the better of
4 the three, the best of the three, when you look at the
5 As, Bs, and Cs.

6 Undoubtedly, new preservatives, or combinations of
7 preservatives, are under study, but any sudden decision
8 to eliminate thimerosal would create a number of
9 potential problems. The first concern is that, at
10 least temporarily, vaccine available would be disturbed
11 and vaccination delayed or omitted.

12 If physicians or state public health authorities
13 insist on immediate access to thimerosal-free vaccines,
14 chaos will ensue. This is not a commercial issue.
15 Each manufacturer will have gains and losses in terms
16 of marketshare. The overall loss is to the vaccine --
17 is to vaccination programs.

18 Second, there is the risk that substitute
19 preservatives will not be as compatible with the
20 vaccines or have less antimicrobial activity and,
21 therefore, lead to an increased possibility of

1 accidents.

2 In the absence of preservatives, filling of
3 vaccine vials must depend more on aseptic filling.
4 Although the technology for aseptic filling grows more
5 and more sophisticated, as illustrated on this slide,
6 which shows a filling apparatus in which the operator
7 operates in a sterile atmosphere through these
8 portholes -- although, as I say, this technology gets
9 more and more sophisticated, it must be admitted that
10 the absence of a preservative deprives us of a safety
11 net to maintain sterility in later use.

12 Fourth, as thimerosal participates in the
13 inactivation and detoxification of Bordetella pertussis
14 in whole cell DTP, elimination of thimerosal would
15 require reformulation and re-evaluation of the product.

16 Fifth, as influenza vaccine requires rapid
17 production of large amounts of vaccine, elimination of
18 a preservative will shift filling to single-dose vials
19 and may slow or reduce influenza vaccine production.

20 Finally, if manufacturers must choose between
21 preparing single-dose vaccines without preservatives

1 and multi-dose vaccines with preservatives, thimerosal
2 or other, in general, they are likely to privilege
3 single doses and therefore reduce the availability of
4 multi-dose vaccines. The effect on vaccination in the
5 developing world may be dramatic, as I am sure John
6 Clements will discuss. In the United States, we should
7 not forget the effects of loss of multi-dose
8 preservatives and multi-dose forms on the function of
9 public health clinics and on the cost of vaccines.

10 The immediate response of manufacturers to this
11 crisis atmosphere will be the usual one. They will
12 respond as fast as possible to a perceived public
13 health and consumer demand. In this case, for
14 thimerosal-free vaccine. As I understand the
15 situation, HIB single-dose and IPV vaccines are already
16 free of thimerosal, and hepatitis B vaccines free of
17 thimerosal will soon be brought to the FDA for
18 approval. DTaP is a mixed bag, but the manufacturers
19 who use thimerosal will seek to bring single-dose
20 preparations without preservatives to the FDA within
21 months.

1 Much will depend on the attitude of the FDA
2 regarding evaluation of existing data. For example, if
3 removal of a preservative is considered to potentially
4 alter stability, there will be delays while real-time
5 stability studies are undertaken by manufacturers and
6 then the results reviewed by the FDA. And, of course,
7 we're looking forward to what Norm Baylor has to say
8 tomorrow.

9 It is interesting that European regulatory
10 authorities met to discuss this issue in April of this
11 year, as many of their vaccines also contain
12 thimerosal. A working group on thimerosal formed by
13 the European Medicines Agency issued documents on the
14 subject. Two of their statements are excerpted on the
15 next slides. As you can read: "For vaccination in
16 infants, the use of vaccines without thimerosal should
17 be encouraged. However, in order not to jeopardize
18 vaccine supplies and immunization programs, it is
19 advisable to introduce requirements for the elimination
20 of organomercurials in vaccines on a gradual basis."

21 And another excerpt, the group concluded that

1 thimerosal should not be banned from medicinal
2 products; however, taking into account the identified
3 and theoretical risks, precautionary measures should be
4 considered. And the most desirable alternative they
5 mention is preservative-free formulations.

6 It is important to stress that until now European
7 countries that also used neonatal hepatitis B
8 vaccination, such as France, Germany, and Italy, have
9 not changed their recommendations. That includes
10 Spain, which, like the U.S., recommends universal
11 neonatal hepatitis B vaccination.

12 So, in summary, what is the manufacturers' view,
13 in quotes, of the situation as interpreted by me.
14 Frankly -- And I think it is important to be frank
15 early in this meeting to promote a useful discussion --
16 I think that FDA did not give manufacturers sufficient
17 warning that thimerosal is no longer acceptable, that
18 panic entered into the deliberations of the AAP, and
19 that CDC was partly handcuffed by regulations that
20 prevented adequate consultation with the ACIP.

21 The published evidence that the thimerosal

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

11 Beyond the factual scientific issues, the process
12 of decision in this matter has been flawed. This
13 meeting should have taken place before a public health
14 decision or a public announcement was made. There
15 should have been adequate consultation and discussion.

16 This point of view probably gives offense to some,
17 and I'm sorry that this should be the case as my
18 remarks are not directed against any person in
19 particular. Reasonable people may disagree on all of
20 these points, and I, for one, am prepared to modify my
21 opinion based on data displayed later in this meeting.

1 However, so far, manufacturers have seen no evidence
2 for a clear and present danger, but, rather, a rush to
3 judgment.

4 At the earlier private meeting called by the AAP,
5 I tried to recommend to the participants a bit of what
6 the French call "Sang-Froid." I found it difficult to
7 give an adequate English translation of the term, but,
8 recently, I came across the French definition given by
9 Denis Diderot in the 18th century.

10 He wrote: "Sang-froid, that quality so necessary
11 to those who govern, without which one would rarely
12 apply justly the means to the circumstances, without
13 which one would lack presence, presence of mind; sang-
14 froid which submits the activity of the soul to reason
15 and which preserves one, in every event, from fear,
16 from frenzy, and from precipitation."

17 I believe we could all benefit from such
18 dispassionate reflection. Thank you.

19 (APPLAUSE)

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

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

14 As far as I'm aware, there's only two cases, and
15 these are patients who had received this in excess of
16 twenty years in these kinds of doses who developed some
17 cerebelli ataxia secondary to accumulated mercury
18 toxicity. Now, the incident is a separate issue,
19 certainly, in regards to also the difference in the
20 immune system of the infant from older children or
21 adults, but in other age groups separate from infants,

1 that seems to be overwhelming data in terms of the
2 safety to support some of what you're suggesting.

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

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

13 **DR. GREENBERG:** In the back? Could you identify
14 yourself?

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

18 **DR. PLOTKIN:** The question that Stan is asking is
19 the use of radiation as a preservative. That's a good
20 question. I must admit ignorance. I have not seen
21 those studies. I imagine that under some circumstances

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

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

8 DR. GREENBERG: Identify yourself, please?

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

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

15 DR. GREENBERG: Any other questions?

16 (NO RESPONSE WAS HEARD)

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

20 (LAUGHTER)

21 DR. PLOTKIN: I'm glad to be able to get off the

1 podium 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
13 to 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
20 think of me both as somebody speaking from a global
21 perspective from WHO, but also as an advocate for a

1 hundred million such children as this every year. This
2 young gentleman is sitting in a cardboard box with a
3 hole cut for his legs and he is very interested in what
4 we're going to say this morning.

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

16 And I must say that I'm delighted being third in a
17 row of three, and I hope you'll find that what I have
18 to say is very synoptic with the previous two speakers.

19 I make no apologies for covering similar ground,
20 although I hope you'll remember my friend from Africa
21 as we speak. And I keep pressing the wrong key. Never

1 mind.

2 Okay. The United States has gone through its due
3 process to identify a problem and take action to remedy
4 it. However, there is a knock-on effect which the rest
5 of the world must bear as a consequence. And what I
6 want to do is to draw out in the next few minutes some
7 of these consequences for you and examine the knock-on
8 effect. And I want to really say how privileged I am
9 to be here, and I feel that I'm looking over your
10 shoulders as you make -- go through this discussion and
11 make some of these decisions.

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

17 Like Stan, I'm concerned with the scientific
18 process which has gone on to date. There is a lack of
19 agreement about the safe cutoff levels for mercury and
20 there's a variance between the control bodies in the
21 United States, and certainly between WHO, as to what

1 those levels should be. And the infant maximum intake
2 level has been extrapolated only.

3 As far as toxic effects go, it's not clear what
4 levels of exposure to mercury in the fetus, the
5 neonate, and the infant are harmful. We know that
6 there are harmful levels, but we certainly don't know
7 at what point we have to be concerned.

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

19 And I should point out that the discussions which
20 have gone over the last two or three months really
21 suggest that possibly we should be looking at a five-

1 fold lower cutoff point for pregnant women and nursing
2 mothers in order to protect the fetal brain.

3 And even though the JFCA committee that met in
4 Rome in June was aware of the issues regarding
5 thimerosal, they were not in a position to offer any
6 stronger guidelines regarding cutoff levels for
7 pregnant women and didn't even trespass into the dark
8 waters of recommending levels for infants.

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

15 A question already asked: Do we need
16 preservatives in vaccines? And the way that things are
17 going in the United States, there's the clear
18 possibility that as you move to monitor those
19 preparations then there may be a possibility that they
20 are not needed. However, this is not the case for the
21 majority of the world.

1 And in tests that we've undertaken recently in
2 vaccines, it is clear that the lack of preservatives
3 pose a serious threat to the integrity of multi-dose
4 vials which have already been opened and penetrated by
5 at least one needle through the cap.

6 These lists vary a little bit depending on who's
7 presenting, but I think we're fairly consistent in
8 identifying some alternatives to thimerosal. 2-
9 phenoxyethanol is -- looks like the forerunner, but we
10 have limited information on comparative effectiveness.

11 Formaldehyde, cresol, possibly others. Phenol, I
12 should draw your attention to, in the WHO regulations,
13 is not permitted any longer.

14 If thimerosal is not available, what alternative
15 strategies are there for developing countries? Well,
16 we can move to a mono-dose vial without preservatives
17 or we can seek a replacement to the preservatives. But
18 as is already pointed out by Stan, there are serious
19 consequences for both options. The product must be
20 reformulated, new clinical data must be presented, and
21 new submission for license must be made, and for

1 vaccine supplied through UNICEF, then a special
2 WHO/UNICEF approval must be processed. All in all, a
3 long time interval before availability of either of
4 these alternatives.

5 You've heard already, and you'll hear I know in a
6 lot more detail, how the regulatory bodies in the
7 United States go through their debates. In terms of
8 WHO, we have an Expert Committee on Biological
9 Standardizations which meets regularly, which is
10 composed of outside experts. Although it is hosted by
11 WHO, it is not an internal committee, it is an external
12 committee, and it results in WHO producing WHO
13 technical report series, which I've already quoted from
14 once.

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

17 "If the vaccine is to be dispensed into multi-dose
18 containers, a suitable antimicrobial preservative shall
19 be added. The amount of preservative in the final bulk
20 shall have been shown to have no deleterious effect" --
21 Never put that on a slide if you have the say it in

1 public --

2 (LAUGHTER)

3 DR. CLEMENTS: -- "on the toxoid or on any other
4 vaccine components with which the toxoid may be
5 combined, and to cause no unexpected adverse reactions
6 in humans. The preservative in its concentration shall
7 be approved by the national control authority and don't
8 include phenol."

9 The other vaccine that we're particularly
10 concerned about is hepatitis B, and the ECBS says about
11 that: "Each final bulk or final lot shall be tested
12 for the presence of preservative. The method used and
13 the permitted concentration shall be approved by the
14 national control authority. The most common
15 preservative used for hepatitis B is thimerosal," and
16 then it goes on to describe the analytical methods.

17 So, in summary, through the expert committee at
18 WHO is saying that the task of the
19 preservative -- the task that the preservative is
20 designated for -- In other words, to be antimicrobial -
21 - must be defined and fulfilled.

1 Again, as Stan has already pointed out, it must
2 not damage the vaccine in any way, like thimerosal and
3 IPV, and it must not damage the human recipients,
4 although that is not spelled out how. The level is set
5 not by WHO but by the national control authorities.

6 Now, what implications has all this to do for the
7 global supply of vaccines? Since Stan has begun to
8 open up this discussion, I need to just clarify for
9 some of you who may not be familiar with it, the
10 majority of the world, particularly developing
11 countries, looks to three main sources to get their
12 supply of vaccines.

13 The first is the local producer, and that may
14 surprise some of you who are not familiar with this
15 subject; secondly, UNICEF-supplied vaccines; and
16 thirdly, they may go directly to the manufacturer and
17 buy directly through them.

18 And if you look at this graph, the red at the top
19 is the local production. I'm sorry I don't have more
20 up-to-date information to show you, but the trend has
21 continued where a large proportion of the world's

1 vaccines are produced in-country and consumed in-
2 country.

3 If you look at this description of DPT sources by
4 WHO region, you can see that in the Eastern/Western
5 Pacific Region and the Southeast Asia Region, a vast
6 proportion of the vaccine is made locally and consumed
7 locally. We'll discuss the implications in a moment.

8 And for hepatitis B, many countries in the
9 developing world have HBV transmission by the neonatal
10 route. In other words, the first week, first two weeks
11 of life are crucial in protecting the infant; and if
12 there is no birth dose of hepatitis B given, then there
13 is likely to be transmission of the virus. And this
14 means that without a birth dose in China, between 10
15 and 15 percent of all births are likely to result in
16 chronic infection.

17 What immediate impact on developing countries
18 would there be if thimerosal were removed from
19 vaccines? As Stan has already said, existing suppliers
20 would be unable to supply such vaccines and supplies
21 would rapidly dry up.

1 Locally-produced vaccines, and remember I've
2 identified them as being a major source in developing
3 countries, would be unable to substitute for this
4 preservative. Local production would either stop or --
5 I'm not sure whether it's worse or about the same level
6 of significance, but they might turn to producing
7 without the preservative.

8 We've mentioned another strategy of moving to
9 mono-dose vial preparations, but at the moment,
10 basically all vaccines in developing countries are
11 drawn from multi-dose vials.

12 The cold chain could not cope with a five- to
13 twenty-fold increase in volume which would be resulting
14 from this. It would double the cost of the cold chain,
15 and result in a cold chain costing around half a
16 billion dollars a year. There would be a six- to ten-
17 fold increase in vaccine prices for these countries,
18 which could not be borne by them. Even if there was a
19 switch to mono-dose, those products still need
20 relicensing.

21 The one hope in the dark tunnel at this moment in

1 this scenario is that we are watching the development
2 of a pouch-and-needle hepatitis B delivery system in
3 its field trials, and there is at least the possibility
4 that that will fill a niche as being a disposable
5 single-dose delivery system.

6 What happens -- The alternatives open to
7 developing countries. They could obtain vaccine
8 through their regular UNICEF supply with a new
9 preservative if a new preservative became available.
10 They could purchase directly from industrialized
11 countries. They could use locally-produced vaccine, or
12 they could use vaccine which is imported in bulk and
13 filled locally, or they could switch to mono-dose with
14 no preservatives.

15 And what about the time and the impact of these
16 decisions they would make? If they waited for a
17 preservative to be introduced into UNICEF vaccines,
18 that is going to be a long wait. If they purchase
19 directly from industrialized countries, not only do
20 they have the wait, but they will certainly have an
21 increased cost. If they rely on locally-produced

1 vaccines, they have to try and obtain the new
2 preservative, perhaps under license, again a long wait
3 and an increased cost. If they go for local filling
4 from bulk purchased overseas and the license, there's a
5 long wait and an increased cost. And if they switch to
6 mono-dose, it may be relatively quick, but it will be
7 far too expensive, both in terms of purchasing the
8 vaccine and in managing the cold chain.

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

19 In summary, then, my Executive Director, Michael
20 Scholtz put out a press release a few weeks ago: WHO
21 will continue to recommend thimerosal-containing

1 vaccines. We see no reason for changing that given the
2 present amount of information and the scientific
3 debate. Mono-dose hepatitis B vaccine will continue to
4 be administered in the birth dose and all the other
5 doses from multi-dose vials. At this point, there is
6 no option about using mono-dose. Although, as I said,
7 a light in the end of the tunnel is the patch-and-
8 needle device.

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

14 One thing I've observed doing this over the last
15 few months is a concern, and I asked the question:
16 Instead of the onus being on the scientist to
17 demonstrate there is a problem, has the onus now
18 shifted to the pro-vaccine community to show that there
19 isn't a problem?

20 And remembering my patron sitting there in Africa,
21 what does it all mean for him or her? Well, there is

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

13 (APPLAUSE)

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

15 Do we have any questions?

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

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

1 **DR. CLEMENTS:** When the United States generated
2 this interest and it went public on the Internet and in
3 the 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
10 happy to say that. So it doesn't seem to have had any
11 impact 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
15 in for the potential use of single-dose or mono-dose
16 vials and 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

1 would need to be purchased at multiple points in the
2 cold chain, but once those are purchased, then that --
3 is that -- I asking, is that a one-time cost and, you
4 know, what is the recurring cost?

5 **DR. CLEMENTS:** Okay. There are two parts to that.

6 It's approximately doubling the cost of the cold chain
7 to half a billion, and most of that would be capital
8 investment, not recurring costs.

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

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

21 The other is, perhaps, related to what Bruce

1 Gellen was asking, which is its influence on
2 policymakers in other countries, particularly the
3 developing nations. Do you see this as an issue?

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

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

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

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

21 John, How do you see moving forward on this from a

1 global perspective? I mean, it seems to me, as you've
2 indicated, it's going to be a long process, and I'm
3 very concerned about the trends, as you pointed out,
4 were to use local producers, and there are a lot of
5 reasons for that, which we -- you may want to elaborate
6 on. But there seems to be, by doing that, an increased
7 need for a preservative if you're going to rely on a
8 variety of local producers, unless somehow GMP, Good
9 Manufacturing Practices, can be upgraded in many of
10 these countries.

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

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

19 But I think our job in WHO is to guide in as wise
20 a way -- I wish I could remember what Stan's quote was
21 -- to have the wisdom to guide countries in making

1 decisions in an appropriate time base.

2 And what we'll be doing is working with the
3 Experts Committee on Biological Standardization to come
4 up with something similar to the European vaccine
5 manufacturers in encouraging a gradual shift towards
6 mercury-free preservatives, but it will be something
7 which is measured in due time and with due
8 consideration of as many factors as necessary.

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

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

1 system in them.

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

3 I'd just like to point out that there's been kind
4 of a subtle fall down the slippery slope here. That is
5 to say, the discussions have started out by talking
6 about limits, tolerable limits, to the amount of
7 mercury, and now we're talking about zero tolerance.
8 So we've now progressed -- I'm generalizing here, of
9 course. We've now progressed to the point where no
10 mercury is tolerable at all, whether it meets EPA
11 requirements or not.

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

18 **DR. CLEMENTS:** Well, I think, Stan, you made a
19 rhetorical statement there which I certainly don't
20 agree with, that we're wanting zero dose mercury. That
21 has not been established in any scientific setting. If

1 may be an emotional response which you're talking about
2 on a slippery slope, but mercury ingestion and
3 environmental mercury that we have around us now make
4 it impossible to think that we'll be mercury-free.
5 What we're talking about is how much mercury is
6 acceptable. That doesn't negate the desire -- the
7 desirability of having mercury-free vaccines, but we
8 certainly are not targeting that as -- that is not
9 necessarily our immediate goal, although it may be our
10 long-term desirability.

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

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

1 consideration been discussed?

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

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

14 Bill?

15 **DR. EGAN:** If I could just make a comment. First
16 of all, thimerosal, or if you want to go on the other
17 side of the Atlantic, thimerosal, has not been banned.

18 So we're not talking about that it must come out of
19 all vaccine. So, you know, thimerosal has not been
20 banned. We are, nonetheless, concerned about the
21 cumulative doses of mercury and we prefer to have

1 mercury-free vaccines and preservative-free vaccines,
2 i.e., single-dose presentations in the United States.

3 We have asked manufacturers for their -- you know,
4 for their plans for elimination of thimerosal and that
5 it'll still be a -- you know, if they cannot eliminate
6 it, to justify it and be allowed where justified. So,
7 you know, we haven't gone to that point of saying, you
8 know, as of such and such a date, mercury cannot be in
9 any preservative -- in any vaccine.

10 **DR. SNIDER:** Dixie Snider. I just wanted to raise
11 one additional point that I think has been implied but
12 really hasn't been made explicit, and that is that I
13 think the -- there is an important issue here around
14 the credibility of immunization programs nationally and
15 globally, and that although it may not be in the best
16 interests of everyone to eliminate mercury entirely
17 because the risk or the price of doing so might be a
18 price we don't want to pay, I think the concern about
19 the integrity of the entire immunization effort, if you
20 will, has been on many people's minds and has been a
21 part of the decision-making process up to this point

1 and will continue to be a part of the consideration
2 here. Not that people do not want to react to
3 scientific information that is available in an
4 appropriate way, but, in addition, when there are
5 choices that can be made to move from a thimerosal-
6 containing vaccine to one which is -- can be found to
7 be just as safe and effective without that agent, then
8 it's to the immunizations programs' advantage to be
9 seen as not adding to the mercury that people are
10 ingesting all the time, not be adding to mercury
11 burden.

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

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

17 I just wanted to make one comment regarding the
18 issue of the timing here, and it was alluded to that
19 this was rather sudden. The issue and concern over
20 thimerosal has been an ongoing discussion, and I think
21 the discussions with manufacturers looking at the

1 reduction and/or elimination of thimerosal is not a new
2 issue. I think some of the aspects which triggered
3 some of the current information that has been discussed
4 has been during the FDA Modernization Act of 1997. We
5 were directed at the FDA to do an evaluation of
6 mercurials in all FDA-regulated products. As part of
7 that initiative we worked cooperatively with the
8 manufacturers to get the data, which is what you will
9 be hearing later in the workshop. The issues are then
10 looking at cumulative levels, as was discussed by Dr.
11 Snider, I think became the issue of concern. The
12 vaccines are believed, when looked at, safe and
13 effective, but when you're looking at cumulative does
14 in small neonate typing, I think the issue and the
15 concern was raised and should be looked into, both from
16 a scientific as well as a public health issue.

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

21 **DR. GREENBERG:** Dr. Plotkin.

1 DR. PLOTKIN: Well, several points. One,
2 actually, in responding to Dr. Zune, I think
3 the -- there is general agreement that mercury is not
4 going to be used in future vaccines. I think the issue
5 is more whether it needs to be removed immediately from
6 currently licensed vaccines.

7 In relation to Dixie Snider's comment, I would
8 like to say that if anti-vaccinationists did not have
9 mercury, they would have another issue, and one cannot
10 prevent them from making hay regardless of whether the
11 sun is shining or not. So I don't think that's really
12 a valid reason for making decisions.

13 Lastly, I don't want to lose sight of the comment
14 by, I think Dr. Wannake from Merck. I am certainly not
15 a vaccine production person, but in looking at the
16 Pharmacopeia regulations, I was struck by their, let's
17 say, apparent excessiveness, and whether one could --
18 And this is actually be considered in Europe, whether
19 one could adopt different criteria which would allow
20 reduction of the concentration of preservatives in
21 vaccines. In other words, that you would require only

1 stasis rather than cetyl activity against 10^5 or 10^6
2 organisms, as Bill Egan mentioned.

3 **DR. GREENBERG:** I know less about this than Dr.
4 Plotkin, but it certainly seems to me that the biologic
5 experiment, there's a lot to be said for that, but it
6 doesn't seem to me that usually contamination should be
7 occurring at quite that level and that you might be
8 able to get exactly the same effect with less than --
9 If somebody in the audience knows how that criteria --
10 what the thought process behind it was, that would be
11 an interesting thing to hear about.

12 Bill?

13 **DR. EGAN:** I can't comment about, you know, the
14 thought process, and it goes back quite a few years, I
15 think somewhere around 1970, when the USP introduced
16 those requirements, their definition of a preservative,
17 but I would like to add again what I mentioned during
18 my talk, that I did think that, you know, those are
19 very stringent requirements and that the -- that in the
20 United States, it is not necessary that a preservative
21 per, you know, the CFR must meet the USP definition.

1 Certainly, that's -- you know, that's acceptable, and
2 it has been, but it's not a requirement that it meet
3 the USP to satisfy the CFR. I did run that through our
4 general counsel.

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

7 **UNIDENTIFIED SPEAKER:** Just one comment. Usually
8 when we're manufacturing, we think on the international
9 level, and, particularly, it's the European
10 Pharmacopeia that is the mandatory one, and their
11 requirements are perhaps even more strict than the USP.
12 therefore, you know, I'm thinking in the international
13 scheme of things, that becomes an issue.

14 Let me give you an example. A few years ago,
15 quite a few years ago, we were working with the
16 Europeans and taking a product that's no longer -- a
17 diluent that's no longer on the market that had a ←
18 preservative in it, and it was a single-dose vial, but
19 there was a very low level of thimerosal in it which
20 would not pass the European Pharmacopeia. And we said,
21 well, basically this is a single dose, it's there as

1 assurance for misuse after it leaves the manufacturer.

2 And they said, well, no, still got to meet European
3 Pharmacopeia.

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

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

9 I just wanted to respond to Stan by saying that I
10 wasn't speaking -- in talking about credibility, I
11 wasn't speaking to try to address issues that anti-
12 vaccine groups might raise because I do realize that
13 there are incredibly an unending list of complaints or
14 charges that could be made.

15 I'm more concerned, though, about scientists at
16 the Agency for Toxic Substances and Disease Registry
17 and the National Center for Environmental Health and
18 the Environmental Protection Agency and others who have
19 expressed concerns about the mercury that we are
20 delivering and was only trying to suggest that, in view
21 of concerns of scientific groups, it is reasonable to

1 consider how we can lower or eliminate the mercury that
2 we deliver through vaccines since people will get it
3 through, unavoidably, a series of food supply.

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

5 **DR. KLEIN:** Jerry Klein, the Boston University.

6 Stan, as a point of information, could you clarify
7 the many products that do not have thimerosal? Now, do
8 they have other preservatives, or are they free of any
9 preservatives? And if so, what is the basis for their
10 success and is it just something that is necessary for
11 the manufacturing products in selected vaccines? As
12 example, there's one pneumococcal vaccine that has
13 thimerosal, as the alternative product does not, and
14 the same thing with amphophilous influenza.

15 **DR. PLOTKIN:** Well, there are many parts to that
16 question. The best table on the list of vaccines
17 containing thimerosal is the one published by the AAP,
18 and I refer to it often. But as Bill mentioned, IPV
19 contains 2-phenoxyethanol because thimerosal will
20 inactivate the polio component. Other than that, I
21 think -- I think, but I'm not absolutely certain, that

1 benzyl alcohol may be in some unusual vaccines, but in
2 terms of common vaccines, I think those are the only
3 two.

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

8 Now, of course, as I stressed, where single-dose
9 presentations are the only form, you can, in fact, do
10 simple aseptic filling with the risks that Bill
11 mentioned.

12 So the choice of whether there's TM in it or not
13 depends on largely what forms are being made, whether
14 bulks have to sit around for some time before they're
15 combined for filling, and issues which relate to the
16 perceived production process and the subsequent use --
17 that is, the subsequent use by physicians -- whether in
18 the single-dose form or in the multi-dose form, and
19 also capacity of the manufacturer to make one or the
20 other.

21 I'm not sure that I've answered your question very

1 precisely, but I -- that's about the closest I can
2 come.

3 UNIDENTIFIED SPEAKER: But there are a number of
4 products that appear to be in multi-dose form that do
5 not have preservatives?

6 DR. PLOTKIN: No.

7 UNIDENTIFIED SPEAKER: So any multi-dose form does
8 have a preservative? ??? where is answer

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

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

14 DR. GREENBERG: If everybody could take their
15 seats, please? In the back, sit down.

16 Okay. We're now going to finish up the morning
17 session. Before we start, I have one question that was
18 -- several people have asked, and I just wondered
19 whether any of the speakers from the morning could
20 answer it, and that was: For multi-dose vials --
21 Measles/Mumps/Rubella is a multi-dose vial and does not

1 have preservative in it -- do people know how the
2 problems of preservation are dealt with in that
3 vaccine? That's the question. Does anyone have an
4 answer? A quick answer?

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

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

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

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

10 (LAUGHTER)

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

16 So the next speaker is Dr. Jeffery Englhardt,
17 Senior Research Scientist at Eli Lilly, who are the --
18 which is the company that makes thimerosal, and his
19 talk will be "Toxicology and Metabolism of Thimerosal
20 in Animals."

21 **DR. ENGLHARDT:** Thank you. I appreciate Dr.

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

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

8 Looking back into the historical literature,
9 thimerosal had a variety of chemical properties that
10 made it very attractive. And one of the things also,
11 as I was reading this literature, is that not all
12 mercuries are alike, and I'd like to retread that again
13 a little bit later in the talk. Now, thimerosal is
14 found to be very water soluble. It was created stable
15 solutions and also compatible with a variety of
16 biological materials. As Dr. Klein mentioned earlier,
17 we were one of the first to be using thimerosal as a
18 preservative in some of our older vaccine days in terms
19 of the diphtheria vaccine. It was also used in some of
20 our other toxoids that were produced back in the '30s
21 and '40s. And as mentioned also, this has been

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

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

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

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

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

19 Oral toxicity in rats has a MLD of about 73 mg/kg
20 and, as you can see, when you look at the rodents and
21 the lagamorphs (sic), there is a disparity in terms of

1 what the bodyweight toxicity is, but the overriding
2 morphological alteration that occurs in these animals
3 is renal necrosis. This is interesting in the fact
4 that this type of toxicity is what has been described
5 most widely with mercuric chloride studies, which is
6 renal necrosis.

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

21 Also as mentioned earlier, thimerosal is a very

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

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

21 I was also surprised to find that there was a two-

1 year carcinogenicity study that had been conducted on
2 vaccine preservatives and thimerosal was included in
3 that particular study, and the outcome of that was that
4 there were no compound-induced neoplasms. It should
5 also be noted that thimerosal does cross the
6 blood/brain barrier. It also crosses the placental
7 barrier. However, there has not been any evidence of
8 turadnogenicity (phonetic) that's been shown with the
9 compound in a study that was conducted with one of the
10 contact lens preservatives.

11 It should also be noted -- And this is one of the
12 gaps that I identified and this is part of the concerns
13 that are raised here in looking at the neonatal vaccine
14 issue -- is that typically now with the pharmaceutical
15 agents, we do what's called a post-natal development
16 study or a Segment III study, and there's nothing in
17 the literature right now that has anything that looks
18 at in utero exposure to thimerosal and in post-natal
19 development in rodents. So we do not have any data
20 that would indicate either a risk or a lack thereof.

21 I did find one article that I found very

1 informative and that was an article published in 1975
2 by Blair, et al., that was looking at the metabolism
3 and excretion of thimerosal in adult squirrel monkeys
4 and this was a chronic study, a chronic daily
5 administration study.

6 Thimerosal, at a concentration of .002 percent,
7 and this is, I believe, in the range of what's used as
8 a preservative in the vaccines. I think that's allowed
9 to go up to about .01 percent. This was administered
10 in two ranges, either 2.2 or 12 micrograms per monkey
11 per day for six months and that the total thimerosal
12 dose was 418 or 2280 micrograms. If you remember, this
13 has a 49 percent of mercury, so this means that these
14 animals received roughly 200 micrograms of mercury or
15 1100 micrograms of mercury.

16 Now, this is a classic tissue distribution study
17 and, unlike what's done with pharmaceutical agents,
18 they had to use atomic absorption to look for the
19 mercury. So the tissues were dissected, analyzed for
20 the presence of mercury and what form was that mercury
21 in and also histologic evaluation of those tissues to

1 see if there were any accompanying morphologic
2 alterations due to the presence of absence of the
3 mercury.

4 The data from this study showed that there was no
5 evidence of toxicity either seen clinically during that
6 six-month administration phase or during the pathology
7 evaluations. There was variation in the mercury
8 concentration in individuals. That is, within those
9 given groups, there was a disparity in how much
10 mercury, even though they were given the same dose by
11 the same period of time, on how much mercury was
12 accumulated in different tissues, but what was of note
13 was that the mercury that was present in the blood and
14 tissues was primarily in the inorganic form and also
15 that the distribution of the
16 tissues -- or within the tissues had kidney as being
17 the primary organ, followed by liver, muscle, brain,
18 and the least of all, in blood.

19 Now, some of this conversion from the organic to
20 the inorganic may lead to the point that I made
21 earlier, that all mercuries are not alike and that

1 within the organomercurials, there is a difference in
2 the stability of that carbon/mercury bond, and I'm
3 hoping that when Mr. Lucier presents later, talking
4 about ethyl and methylmercury that he will be striking
5 on that.

6 It also should be noted that the ethylmercury
7 compounds, particularly thimerosal, will also undergo
8 this biotransformation of organic to inorganic in human
9 tissues, and that was described in a report by Suzuki
10 in 1971.

11 As I mentioned, the kidney had the highest
12 concentration, and you can see we've got over 3000
13 nanograms -- These are the mean values that were
14 presented in this article -- and that the predominant
15 form that was present within the kidney tissue was
16 inorganic. And as you go through, you can see that
17 from the kidney, as you move down, there is a quite a
18 disparity between the average values that were present
19 in the brain in terms of inorganic mercury and what was
20 present in the major excretory organ and very little
21 present in the blood.

1 Again, there was no evidence of toxicity seen
2 clinically or evidenced morphologically that the
3 presence of this mercury was causing any deleterious
4 effect on these animals.

5 One thing that was brought out in this article is
6 they mentioned that a critical brain level of mercury
7 range from 3 to 9 micrograms per gram in the brain to
8 cause toxic effects. What should be noted is that even
9 though there were differences among all these animals,
10 the highest level in the high-dose animals was only 245
11 nanograms per gram in the brain and 73 percent of that
12 was organic. Now, what this article did not provide us
13 was elimination data. We do not know how rapidly the
14 mercury that was within the animals was removed.
15 However, one could extrapolate that since this is
16 present primarily in an inorganic form that it would
17 likely follow the types of kinetics that have been
18 described experimentally for inorganic mercury. There
19 was an abstract presented at the 1998 Society of
20 Toxicology meeting looking at a population
21 pharmacokinetic study following mercury vapor exposure

1 in humans that determined that the half-life in the
2 kidney compartment was roughly nine days. So if you
3 start thinking of the amount that is given as part of a
4 preservative relative to the accumulation that was seen
5 over six months daily administration in this study,
6 there may be some disparities in terms of toxicity
7 relevance from what we know in the animal studies.

8 And one of the differences between methyl and
9 ethylmercury, if this is -- and also the inorganic
10 mercury is that if this is present inorganic form, it
11 should be eliminated more rapidly than what's known for
12 methylmercury. It's known that the inorganic forms are
13 removed more rapidly than methyl. Also with inorganic,
14 about 50 percent of the material is eliminated in the
15 feces without enterohepatic circulation which known for
16 the methyl form.

17 In summary, I'd just like to say that the animal
18 studies that have been conducted, even though they are
19 very limited, have looked at doses that are greater to
20 or equal than what's present in preservatives. What we
21 did find in terms of the acute lethal dose is that

1 there seems to be some correlation between the one
2 human study -- or one human case report that I
3 uncovered and what the animal studies indicate and that
4 the presentation does look very much like what's been
5 described in the literature for the mercuric chloride
6 studies and that renal toxicity is the primary
7 alteration and this occurred only at high doses in all
8 of these animal studies.

9 This particular change may also be consistent with
10 the kidney being the primary organ of accumulation that
11 was seen in this study by Blair. It should also be
12 noted that at no time in any of these animal studies
13 that have been described was there any evidence of
14 neurotoxicity or morphologic alterations anywhere
15 within the brain.

16 This is a very exquisite dermal irritant and
17 allergen and as I went through the literature, I found
18 a plethora of reports on allergic reactions and this is
19 a very important issue in its own right, not to
20 downplay anything relative to the accumulation of
21 mercury, but the mercury itself is present within blood

1 and tissues and generally within the -- as an
2 inorganic. From that standpoint, its particular
3 relevance in terms of cumulative effects and, again,
4 its tissue distribution, I hope are considered as part
5 of the toxicity information when you're deliberating
6 how to look at alternatives and really what the
7 toxicity issues are with thimerosal.

8 So that's the end of what I have. Again, it's
9 over old, very limited, and in difficult-to-find
10 places, and I thank of our archivists for having some
11 of these older articles around. If it weren't for
12 them, I probably would not have uncovered some of this
13 information.

14 DR. GREENBERG: Thank you, Dr. Englhardt.

15 (APPLAUSE)

16 DR. GREENBERG: Well, working with little data
17 hasn't hurt most of you in the past.

18 DR. KIM: Dr. Kim, from Los Angeles. You provided
19 data, I think, primarily in adults. Are there any data
20 available in either experimental animals and inputing
21 rodents and monkeys, primarily looking to the tissue

1 distribution and metabolism in babies, neonates?

2 DR. ENGLHARDT: No, there's no neonatal data that
3 I've been able to uncover. The last article for an
4 animal study that I was found was that 1976 article by
5 Blair. I have not been able to uncover anything in
6 terms of new studies that have been published. We did
7 have one unpublished report on the teratology study,
8 but nothing in terms of postnatal development or
9 exposure in the neonate.

10 DR. KIM: It seems you indicated that mercury
11 compound crosses the blood/brain barrier and the
12 placenta barrier. I guess at this juncture it is
13 unknown whether the exposure of a single dose or
14 chronic doses may have a deleterious effects on the
15 neurodevelopmental aspects?

16 DR. ENGLHARDT: That's correct. That's one of the
17 gaps that I identified, the lack of the postnatal
18 development study. That's typically where we would
19 pick these things up. You expose the fetus as you
20 would in the teratology study but allow the delivery to
21 take place and then do the behavioral assessments

1 postnatally. And no data relative to that was present
2 in any of the literature packs. Again, that would get
3 after your question.

4 **UNIDENTIFIED SPEAKER:** (inaudible) and Disease
5 Registry.

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

9 **DR. ENGLHARDT:** I did not see any kinetic data
10 other than this biotransformation will occur, not only
11 in circulation but also in tissues. The report by
12 Suzuki was cited in an article by Dr. Clarkson and the
13 original article was in Japanese and I was unable to
14 understand that, but I believe that kinetics were
15 discussed because there were x/vebo (phonetic) studies
16 that were also cited. Unfortunately, I can't give you
17 a kinetic number for that. All we know is that there
18 is conversion, but how rapidly that occurs, we don't
19 know.

20 **DR. KILBOURNE:** The acute toxicity studies that
21 you showed -- I'm sorry. My name is Ed Kilbourne from

1 NC -- from CDC, NCEH.

2 The acute toxicity studies that you showed, were
3 those LD 50's?

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

5 DR. KILBOURNE: And I'm sorry, but I didn't get
6 the units of the organ-specific concentrations that you
7 showed later on.

8 DR. ENGLHARDT: Those are nanogram per gram.

9 DR. KILBOURNE: Okay. Thank you.

10 DR. ENGLHARDT: So even much less than what was
11 presented earlier from the Faroe Islands study because
12 those were all microgram per gram concentrations.

13 UNIDENTIFIED SPEAKER: (Inaudible) Is there any
14 evidence or is there anything known whether the
15 compound, the ethylmercury, is covalently bound to
16 proteins?

17 DR. ENGLHARDT: There is nothing on covalent
18 binding to proteins. We do know that the mercuric ion
19 will react with subhydrol groups. So if you figure the
20 number of sistines that may be present in any given
21 protein, you can have oxidation of that subhydral

1 reading to a denaturative event, but there's nothing
2 that says that there is covalent binding to that
3 particular protein. Even some of the in vitro studies
4 haven't addressed that question.

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

6 (NO RESPONSE WAS HEARD)

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

11 **DR. BALL:** I would like to thank Dr. Myers and the
12 other organizers for the opportunity to discuss the
13 findings of our review on the use of thimerosal in
14 vaccines.

15 Specifically, what I will be reviewing today is
16 the FDA safety assessment of thimerosal in vaccines.
17 We concentrated our review on vaccines that are used in
18 infants because this is population that is receiving
19 the largest dose of thimerosal per kilogram and,
20 because the developing brain of infants, may be
21 affected by a mercury-containing compound, including

1 preservatives.

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

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

20 This act had three components. The first was to
21 provide Congress with a list and analysis of the food

1 and drugs containing mercury. This is the only
2 component of the FDAMA that had a statutory deadline.
3 The statutory deadline was two years from the date of
4 enactment, or November 18th, 1999.

5 Under this provision, the FDA issued two call-for-
6 data in the Federal Register that was directed at
7 vaccine manufacturers, and this was a voluntary call
8 for information. The first one was published in
9 December of 1998 and the second was published in April
10 of 1999. The latter had a due date of June 1st, 1999.

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

19 In terms of the relevance of this, well, you know,
20 it's been mentioned that there's been an increase in
21 the number of vaccines recommended for routine use in

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

4 One thing I want to emphasize, you know, I think
5 we've all heard about the lack of data both in humans
6 and in animals regarding thimerosal. But one thing
7 that we kept in mind is that the absence of data of a
8 harmful effect for a low-level exposure of infants to
9 ethylmercury is not the same as data demonstrating the
10 safety of thimerosal, particularly the type of effect
11 that we're likely to observe. It's not likely to be
12 clinical toxicity, it may not even be pathological
13 toxicity, but it may be cognitive effects that we are
14 concerned with, such as observed with methylmercury.

15 I put this slide up to remind us that life was
16 simpler not too long ago. This schedule was taken from
17 the 1988 Red Book -- This was when I was a pediatric
18 resident -- and it demonstrated that during the first
19 six months of life, infants only received five vaccines
20 and only three of which, the DTP, contained thimerosal.
21 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,
3 and AAFP Routine Childhood Immunization Schedule. As
4 you can see, we have several new vaccines in the
5 infants' schedule, including hepatitis B and HIB
6 vaccine during the first six months of life.

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

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

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

1 latter two, neurotoxicity and nephrotoxicity have only
2 been observed in very high doses and also with regard
3 to inadvertent overexposure of thimerosal.

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

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

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

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

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

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

1 that he was maximally ill, as well as developing
2 polyneuropathy and respiratory failure.

3 And to summarize these studies, some of the
4 effects that were seen were local necrosis, acute
5 hemolysis, disseminated intravascular coagulation,
6 acute renal tubular necrosis, obtundation, coma, and
7 death.

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

15 It's important to remember that here
16 that's -- you see that most of the reports involve
17 local hypersensitivity reactions. The most common
18 vaccine that was identified was hepatitis B. And it's
19 important to realize the limitations of this data.
20 Causality cannot be inferred both because of the
21 passive nature of VAERS and the many antigens present

1 in vaccines in addition to thimerosal.

2 Because of this lack of data on low-dose
3 thimerosal toxicity, we made the conservative
4 assumption, and perhaps controversial assumption as
5 we'll hear and we've heard already, that ethylmercury
6 toxicity was analogous to methylmercury toxicity.
7 Since thimerosal is metabolized to ethylmercury, we
8 looked for the -- for evidence of chronic effects of
9 methylmercury to identify risks from chronic low
10 exposure to thimerosal. Obviously, this assumption
11 will be the point of the next session and the
12 discussion in much of this workshop.

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

1 On the basis of these -- the studies that I
2 mentioned with regard to methylmercury, several
3 organizations have set safe limits for exposure from
4 methylmercury, primarily from the diet, and these have
5 all been alluded to. EPA has set a limit of 0.1
6 microgram per kilogram per day; ATSDR has set at .3
7 micrograms per kilogram per day, with the FDA at .4
8 micrograms per kilogram per day.

9 And I think one thing that I noted when we -- we
10 noted when we did the review was that the EPA report --
11 sent a report to Congress that was submitted in
12 December of 1997, only made a very tangential reference
13 to mercury in vaccines, and the mercury toxicological
14 profile that was published by the ATSDR also did not
15 look extensively at the issue of ethylmercury from
16 thimerosal and vaccines.

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

19 First, as we mentioned, the assumption was that the
20 methylmercury toxicity is the same as ethylmercury, and
21 this will be discussed and debated.

1 Secondly, we did not take into consideration
2 differences in pharmacokinetics, such as the route of
3 administration. Methylmercury is ingested orally on a
4 usually low-level basis, whereas the route of
5 administration for thimerosal is intramuscular, kind of
6 in a bolus-type exposure.

7 Also, there is, as I mentioned, differences in
8 daily schedule and the magnitude of doses and the
9 possible differences in elimination, and we've already
10 heard about some of those differences.

11 So next what we looked at was what the exposure of
12 infants to methylmercury is from the U.S. Recommended
13 Vaccination Schedule and how it compares to suggested
14 limits for safe intake of methylmercury.

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

19 And as we have heard, thimerosal is 49.5 mercury by
20 weight in the form of ethylmercury. An example of the
21 calculation of the amount of thimerosal -- I'm sorry,


1 the amount of mercury can be done this way. Hepatitis
2 B vaccine is .005 percent thimerosal and is added in
3 the final concentration. It's 15 micrograms of
4 thimerosal per 1 ml, or 25 micrograms of thimerosal per
5 half and ml, which would translate into 12.5 micrograms
6 of mercury for a half-a-ml dose.

7 These are the U.S. licensed vaccines containing
8 thimerosal. We've all seen this in the AAP interim
9 report. There is additional vaccines that are -- that
10 contain thimerosal, I think as was pointed out.
11 Influenza, all of the vaccines contain thimerosal. In
12 addition, there is one pneumococcal vaccine that
13 contains thimerosal and one that does not.

14 This list is a list of thimerosal-free U.S.
15 licensed vaccines that are given routinely in infants
16 and children. This is not an exhaustive list.
17 Obviously, there are more vaccines that do not contain
18 thimerosal. But you can see DTaP, there is one. HIB,
19 several preparations. There's a combination
20 HIB/hepatitis B. Then there are these additional
21 vaccines. There are no U.S. licensed thimerosal-free

1 products for these vaccines.

2 So next what we did was, we calculated the maximum
3 of exposure of thimerosal from vaccines and infants
4 less than or equal to six months of age. And at six
5 months, according to the recommended schedule, an
6 infant may receive three DTaP vaccines, three Hib
7 vaccines, three hepatitis B if it's given on the
8 schedule in which the last dose is at six months, and
9 in selected populations, influenza vaccine may be
10 given. I didn't include this in the final calculation
11 except in the bracketed form. But as you can see, the
12 total amount -- the total maximum exposure from the
13 U.S. schedule would be 187.5 micrograms.

14 My apology to Dr. Bernier in advance for this 
15 slide. I think that this can be misinterpreted and
16 overinterpreted, but I just wanted to say that the
17 reason why we performed this exercise is because of the
18 lack of data that we had. And what we did here is, we
19 used the suggested limits for safe intake for
20 methylmercury from the EPA, ATSDR, and FDA that was
21 previously shown, and it calculated the amount of

1 methylmercury for safe intake during the first six
2 months, or first 26 weeks, to look at what the maximal
3 exposure would be in that six weeks -- six months.

4 And we calculated this for the 5th, 50th, and 95th
5 percentile for female infants, which provides the most
6 conservative estimated limit of intake. As described
7 by these box figures, only EPA guidelines were exceeded
8 using the assumptions listed here.

9 Since these calculations are hypothetical, we
10 looked to find data that mercury levels can be
11 increased at vaccination. This study was found in an
12 abstract in "Clinical Toxicology" last year. A
13 manuscript based on these data has recently been
14 accepted for publication by General Pediatrics. This
15 was done at Emory, and I think Dr. Plotkin had already
16 mentioned this, but they looked at 15 pre-term infants.

17 Mean weight was at 748 grams for those infants and
18 five term infants with a mean weight of 3.5 kilograms.

19 These infants received hepatitis B within the first 48
20 hours of life, as was the practice for all pre-term
21 infants in that hospital even though that did not agree

1 with the AAP recommendations.

2 Of note here, as was previously noted, was an
3 increase in mercury levels seen post-vaccination when
4 compared with pre-vaccination, and this change was more
5 noticeable in the pre-term infants. And I think that
6 there can be problems with the methodology of this
7 study, but I think the change here is what is salient.

8 And we put up this slide to show that there is a
9 minimum exposure of mercury from vaccines given to
10 infants in the U.S. schedule. For instance, less than
11 six months, you can -- there can be a total of zero
12 given if you utilize this certain schedule with certain
13 products.

14 Of course, infants with hepatitis B surface-
15 antigen-positive mothers or mothers of unknown status
16 would still receive hepatitis B at birth.

17 In conclusion, we found that published reports of
18 thimerosal toxicity in the form of local
19 hypersensitivity reaction at the doses found in
20 vaccines, that there was evidence of acute
21 nephrotoxicity and neurotoxicity at very high doses.

1 Thimerosal as a preservative in vaccines given in the
2 first six months of life may result in the intake of
3 ethylmercury that exceeds the EPA safe limits of intake
4 for methylmercury, recognizing all the caveats that we
5 -- that were previously stated. And, finally, infant
6 exposure to mercury from vaccines may be avoidable by
7 the use of thimerosal-free products.

8 And I wanted to acknowledge the contributions of
9 Dr. Bolger from Center for Food Safety, Dr. Baylor, and
10 Dr. Goldenthal, as well as the other participants in
11 this review, Dr. Ball and Dr. Pratt.

12 (APPLAUSE)

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

14 We have some time for some questions. Dr.
15 Plotkin?

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

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

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

3 DR. PLOTKIN: Yes.

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

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

8 DR. BALL: Uh-huh (affirmative).

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

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

11 DR. PLOTKIN: Six months. And the number of
12 vaccines, then, up to the six-month visit were
13 calculated?

14 DR. BALL: Right.

15 DR. PLOTKIN: Is that right?

16 DR. BALL: Right. And that is assuming that on --
17 that at the six-month visit, you know, with the maximum
18 exposure, that they would have received all of the
19 thimerosal-containing vaccines at that visit.

20 DR. PLOTKIN: My question basically is: Would it
21 be, in your view, more or less logical to use seven

1 multiplication of micrograms per kilogram per day, if
2 you use seven months --

3 DR. GREENBERG: You have more days.

4 DR. PLOTKIN: Right, there are more days.

5 DR. GREENBERG: Well, then if you use eight
6 months, you have more days --

7 DR. PLOTKIN: Agreed, agreed.

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

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

20 DR. GREENBERG: Is there somebody back there?
21 Yeah. Thank you.

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

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

11 **DR. GREENBERG:** Can we have the lights back on?
12 Thank you.

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

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

19 (LAUGHTER)

20 **DR. CLARKSON:** This is very similar to what's been
21 talked about as to how frequently these infants get the

1 thimerosal. The assumption is, from my colleague from
2 FDA, that there's a vaccine at birth where they get
3 about 12.5 micrograms. There's a vaccine at two months
4 where they get 62.5, one at four months where they get
5 about 50, and one about six months where they get about
6 62. I'm indebted to Dr. Halsey, I think, for some of
7 these numbers here.

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

18 The two lines, one is for the very low bodyweight
19 infants, three standard deviations below the normal,
20 and the other is for the 95 percentile and that's -- A
21 key calculation in this is whether or not any excretion

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

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

17 The toxic effects of ethylmercury on growing
18 infants, as has been pointed out, is unknown, but with
19 methylmercury effects have not been seen in populations
20 at 20 or 25 parts per billion, but may have been seen
21 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,
4 I'm a little bit confused about your description of
5 that 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..
12 There 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
21 simple question: In the tables and the graphs I was

1 looking at, I'm not clear on what's being compared. As
2 I recall your calculations -- but the micrograms you
3 were coming up with were -- in thimerosal were
4 micrograms of mercury.

5 DR. BALL: Exactly.

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

8 DR. BALL: Methylmercury.

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

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

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

14 DR. BALL: Right.

15 DR. SNIDER: But your calculations were actual
16 micrograms of mercury?

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

18 DR. SNIDER: So are you comparing ethylmercury to
19 methylmercury or --

20 DR. BALL: Yes.

21 DR. SNIDER: -- ethylmercury to methylmercury?

1 DR. BALL: Ethylmercury to methylmercury.

2 DR. SNIDER: In micrograms?

3 DR. BALL: In micrograms.

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

6 DR. BALL: Right.

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

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

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

17 DR. BALL: Yeah, that's an excellent point. In
18 the calculations, we were assuming no other exposures.

19 And, in fact, infants are exposed to mercury from
20 other sources, even infants that aren't eating tuna
21 fish sandwiches, but maybe getting exposed through the

1 breast milk, or, prenatally, have mercury levels, as
2 you saw in the abstract, probably also related to
3 either ingestion of fish in the mother or from dental
4 amalgams.

5 DR. MAHAFFEY: And is there any effort to look at
6 these additional sources of mercury and incorporate
7 them in the cumulative exposure to mercury that you've
8 described from the vaccine?

9 DR. BALL: You know, there weren't any references
10 that I was aware of that had good data on the
11 alternative exposures. So I think that would require
12 an effort with the various agencies that do have
13 expertise in looking at those other exposures.

14 DR. GERBER: Gerber, NIAID. I just have a
15 question for Dr. Clarkson.

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

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

21 DR. ROGAN: I'm Walter Rogan from NI Environmental

1 Health Sciences.

2 As Dr. Plotkin pointed out, the choice of the
3 denominator for time is kind of arbitrary and
4 scientifically, I guess, it would depend on your model
5 for how you think toxicity is occurring. And although
6 I think it could be argued that toxicity is directly
7 related to cumulative exposure, I think that for this
8 class of compound that, you could also make an argument
9 that toxicity is related to peak excursion. So just an
10 argument, it could be made to go in the direction of
11 seven months, or eight months, or nine months. The
12 argument could be made to go in the direction of one
13 day and how high you got on the day of vaccination. So
14 it's not a -- it's not a -- the sixth-month is not a
15 maximum in terms of consideration of toxicity. It's
16 just sort of an intermediate level that they, you know,
17 chose to display.

18 **UNIDENTIFIED SPEAKER:** Dr. (inaudible) from CBER.

19 Just a point of clarification. The EPA numbers are in
20 micrograms per kilograms per day?

21 **DR. BALL:** Correct.

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

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

9 **UNIDENTIFIED SPEAKER:** So one of the percentiles
10 was about 400 micrograms. That was micrograms per
11 kilogram bodyweight?

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

14 **UNIDENTIFIED SPEAKER:** Yes.

15 **DR. BALL:** Those calculations were based on the
16 total safe intake that you would calculate for that
17 weight of infants. So if it was, for example, 5th
18 percentile infants, you would use that weight to reach
19 that total maximum level, using the analogous EPA,
20 ATSDR, or FDA standards or guidelines.

21 **UNIDENTIFIED SPEAKER:** That wasn't clear in the

1 presentation. Thank you.

2 **DR. GREENBERG:** We have a minute left for a quick
3 question.

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

5 Leslie, just in your review, what proportion of
6 vaccines in the first six months are actually
7 distributed in multi-dose vials?

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

10 **DR. GREENBERG:** We now have thirty seconds for one
11 more question. Last question.

12 **DR. FISHER:** Yes. Barbara Lowe Fisher with the
13 National Vaccine Information Center.

14 I'd just like to congratulate the FDA on
15 performing this analysis and for taking the action that
16 it did to ask the manufacturers to take thimerosal out
17 of the vaccines. I think that the public expects a
18 strong and effective FDA, and that this kind of action,
19 where it may temporarily cause questions about vaccine
20 safety, in the long run, it's going to instill
21 confidence and trust in vaccines and in the system.

1 I have one question. On your total of 187.5 for
2 the vaccines in the first six months that are given,
3 you used DTaP, three doses for DTaP for American
4 infants. What would the total be if DPT were used,
5 because some infants are still getting DPT?

6 DR. BALL: It's the same.

7 DR. FISHER: The same thing?

8 DR. BALL: The same amount.

9 DR. GREENBERG: Okay. On that note, I'll call the
10 meeting to an end. I'd like to thank all the speakers
11 who did a great job.

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

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

15 DR. GREENBERG: Well, this afternoon we're moving
16 onto a couple of other important areas, and the first
17 is going to be the organomercurials, and we have two
18 substantial talks. The first is by Dr. George Lucier,
19 who is the Director of the Environmental Toxicology
20 Program at the NIH, and he's going to talk to us about
21 "Ethyl and Methylmercury: Pharmacokinetics and

1 Toxicology."

2 DR. LUCIER: Thank you. I think. Actually, this
3 invitation to speak here was accepted by my office
4 staff when I was vacationing and camping in the
5 Adirondacks and not accessible to any phone. So Martin
6 coerced my office staff into me accepting this, but I'm
7 glad they did. I think it's an appropriate activity
8 for me to participate in.

9 I believe the reason that I was asked to give this
10 presentation is that beginning in 1997 -- I should
11 point out, first of all, that I'm not a mercury
12 researcher, although I did have a couple of papers back
13 in the early 1970s. I have a research group, but it's
14 in receptor-mediated talks against dioxins and
15 estrogens and so forth. But my involvement with
16 methylmercury emerged in 1997 when I was asked to chair
17 an interagency review of EPA's report to Congress,
18 which, of course, was due in the end of 1997. I was
19 assured that this activity would only last two months.

20 But while this was going on, ATSDR released a draft
21 toxic profile. Phillipe Grandjean published his papers

1 in neurobehavioral changes observed in the Faroe Island
2 children exposed prenatally to methylmercury, and a
3 number of other activities emerged that really called
4 for attempts to harmonize across federal agencies what
5 the science was telling us and what it wasn't telling
6 us regarding methylmercury, particularly as it relates
7 to developmental neurotoxicology.

8 These activities led to a workshop that we had in
9 North Carolina in 1998, the fall of 1998, about eight
10 or nine months ago. In that, we addressed in a very
11 rigorous way the major studies that had been used in
12 health assessments for methylmercury toxicity. We had
13 remarkable cooperation from the interagency committee,
14 including EPA, ATSDR, FDA, NOAA, the relevant parts of
15 CDC, and other agencies as well and equally remarkable
16 cooperation from the major investigators who's studies
17 we were reviewing. Tom Clarkson, who's here, and
18 showed one of his overheads this morning, which I
19 thought was particularly insightful, as well as
20 Phillipe Grandjean and Donna Merguler, who is
21 conducting some studies in the Amazon.

1 That's my name and where I'm from. My
2 presentation will be, in a sense, two parts. And the
3 first part is a summary of the interagency activities
4 that we've had regarding methylmercury, particularly
5 the areas of agreement and the findings that emerged
6 out of our workshop in 1998.

7 And the second is what we know, and that's written
8 very small, it probably should be written smaller, and
9 don't know About ethylmercury." That'll be a shorter
10 part of the presentation because, as you heard this
11 morning from a number of the speakers, there just isn't
12 too much information out there on ethylmercury. I'll
13 discuss a few issues that perhaps weren't presented
14 this morning.

15 The purpose of the workshop was to discuss and
16 evaluate the major studies, epidemiologic studies,
17 associating methylmercury exposure with an array of
18 developmental measures in children. It was in response
19 to the requirement that the emerging data from the
20 Seychelles and Faroe Islands undergo a level of
21 scrutiny beyond journal peer review if they are to be

1 used in policy setting.

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

12 This was really done under the impetus of the
13 White House Science Office, the Office of Science
14 Technology Policy. Fran Sharples (phonetic) there was
15 the point person. It involved a number of different
16 agencies shown here. I hope you can read it okay. A
17 number of institutes, agencies within DHHS; the NIEHS,
18 which is where I'm from, Bill Raub's Office of the
19 Assistant Secretary for Planning and Evaluation, and,
20 of course, he'll give the next presentation and share
21 the panel discussion; parts of CDC; ATSDR; FDA; again

1 EPA; NOAA; OSTP; and also the Office of Management and
2 Budget who was involved in this.

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

12 First of all, a number of key issues that we kept
13 in mind as we went through the interagency
14 deliberations. I think it's important to point out
15 here that we hear a lot about interagency differences,
16 particularly in regards to the methylmercury issue. It
17 is clear that we do differ. Agencies do differ in some
18 respects, but there are much more areas of agreement
19 than there are areas of disagreement, and let me go
20 through some of these issues that we are cognizant of
21 before the workshop began.

1 One, methylmercury is a developmental neurotoxin
2 in people. There's multiple publications, from
3 Minamata, Iraq, and others to document that. The
4 developing fetus is roughly ten times more sensitive
5 than adults. This is a rough estimate, but probably
6 not too bad of one. I think Tom Clarkson made that
7 original estimate, and from my read of literature it
8 can't be too far off.

9 The relative sensitivity of infants to
10 methylmercury is unknown, but they are likely more
11 sensitive than adults. We really don't have
12 information in infants. We have to keep in mind that
13 the central nervous system and the brain is still
14 undergoing assembly and it's likely it would be
15 sensitive to toxic insult, but we really have very
16 little information, nothing near the extent that we
17 have for prenatal exposures of the developing fetus
18 also for adults. We just don't have much for infants.

19 Effects -- This is a no-brainer. Effects at low
20 level exposures are difficult to evaluate.
21 Methylmercury is ubiquitous and nearly everyone has

1 some exposure. Kate Mahaffey brought that point up in
2 the question and answer to the last presentation, that
3 virtually everyone in this room has some degree of
4 methylmercury in their bodies. So any additional
5 exposure that's received -- and infants have some as
6 well through lactational exposures and other sources.
7 Anything we receive is really an incremental exposure
8 to what's already there. So we need to be especially
9 cognizant of the issues related to cumulative health
10 assessments from the multiple sources of methylmercury,
11 mercury in vaccines only being one of them.

12 Finally, initial efforts to establish safe
13 exposure levels acknowledge the need for further
14 studies in populations with low levels of exposures.
15 And that's really what led, back in the 1990s to early
16 1990s, funding for the studies in the Seychelles and
17 the Faroe Islands, because of a need to have this
18 information after seeing that the developing fetus was
19 really at risk based on the data from Minamata and also
20 from Iraq.

21 The workshop that we had was structured around the

1 deliberations of five panels, and these are five panels
2 that were basically external to the federal government.

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

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

21 Major studies that we looked at was Iraq, where

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

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

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

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

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

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

1 important to note that the follow-ups continue in both
2 of these studies with Tom Clarkson's group, as well as
3 with Phillipe Grandjean in the Faroe Islands.

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

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

19 I was just reading in the, flying up here this
20 morning, USA Today, and there was an article about
21 Andrew Jackson and why he died, and some people, I

1 guess, had theorized -- I hadn't known that -- that he
2 had died of mercury poisoning. But 200 years later,
3 nearly 200 years later, they analyzed his hair and
4 found there's not enough mercury in Andrew Jackson's
5 hair to account for his death. So it has to be a
6 pretty good marker of exposure to be used 200 years
7 later to help ascertain the cause or what was not the
8 cause of death in the case of Andrew Jackson.

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

1 differences in results between the Faroes and the
2 Seychelles, particularly when you consider that we're
3 looking at windows of sensitivity for the developing
4 nervous system.

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

16 Now, getting to the study design issues, there was
17 one here actually was left off of the slide that should
18 have been first, and that's the neurobehavioral
19 endpoints. As I had mentioned earlier in the outcome
20 slide, the Seychelles Islanders were monitored for more
21 global measures of neurological function, whereas the

1 Faroes were looked at for more domain-specific effects:
2 memory, attention, language, these sorts of things.
3 Many of the panelists felt that these were like
4 comparing apples and oranges, and I think everyone on
5 the interagency committee and the scientists themselves
6 agreed that they were really measuring different
7 endpoints of neurobehavioral function. So this could
8 very well explain the differences.

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

16 Another one that was discussed in great detail:
17 selection bias. This was a potential concern in the
18 Seychelles studies because some individuals -- I think
19 39 or something of the 79 -- were excluded because of
20 debilitating conditions. Thorough analysis of that
21 suggests that the selection bias was really not an

1 issue in explaining the results. The panel, I think,
2 felt almost unanimously on that issue.

3 Effects of culture and language were discussed in
4 terms of the questionnaires, usually going back and
5 forth between English, Creole, and French, and
6 Scandinavian in the Faroes study. Again, the panelists
7 felt that this was not a major issue.

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

19 Order effects and effects of tests administration,
20 as I recall, in the Seychelles study they gave the same
21 order to each of the individuals in terms of the

1 administration of the test. In the Faroes, I think
2 they had four predetermined orders of how the tests
3 were administered, and that wasn't really controlled
4 for or dealt with in the model analyses that evaluated
5 the results. So this was a potential issue of concern
6 that the panelists raised regarding the Faroes data.

7 Confounders and data analysis issues, in the case
8 of the Faroes, PCB exposures were also occurring. As
9 most of you know, PCBs are also developmental
10 neurotoxicants. They affect some of the same
11 parameters as methylmercury effects regarding the
12 developing nervous system.

13 The PCBs were measured in both the Faroes and the
14 Seychelles. There was significant PCB exposure in the
15 Faroes, essentially none in the Seychelles. So it's a
16 potential confounder for Faroes but not the Seychelles.

17 The neurobehavioral endpoints subgroup of the panel
18 said that they did not feel that the PCBs could -- are
19 really confounding the results that were observed, even
20 though they could have some effect on them.

21 Selenium, I knew selenium was a messy issue going

1 in, and it still is. Some people think it affects one
2 way, other people think it affects the other way, but
3 everyone agreed that it would be important to use that
4 as part of the analyses of the data, and that wasn't
5 done.

6 Likewise, a number of dietary nutritional factors,
7 the omega-3 fatty acids, which are beneficial to brain
8 development need to be looked at in subsequent studies,
9 as well as a number of nutritional and dietary data
10 that really weren't collected in the studies that have
11 been published to date.

12 Genetic differences is potentially important.
13 There may be ethnic differences in responsiveness, but
14 given our lack of information about mechanism of action
15 for developmental neurotoxicity for methylmercury, or
16 PCBs for that matter, we're really not in a good
17 position of pinpointing particular differences in gene
18 activation pathways and so forth, that could possibly
19 account for these differences.

20 Influence of covariants, in general, the panel
21 felt that the Seychelles tended toward a slight

1 overcontrolling and the Faroes a slight
2 undercontrolling. Some particular issues that were
3 raised were maternal smoking, which even though 40
4 percent of the women smoked in the Faroes, this was not
5 controlled for in the analysis.

6 Birth weight, that was controlled for in the
7 Seychelles study, but birth weight could be associated
8 with a methylmercury exposure in the development
9 effects. So, perhaps, that could have influenced the
10 results and minimized the ability to detect an effect
11 if it was there.

12 Town versus rural residence wasn't accounted for
13 in the Faroes study.

14 To make a few brief points about the studies in
15 experimental animal models, basically, they were in
16 pretty good concordance, both qualitatively and
17 quantitatively, with what was seen in people. There
18 have been effects of methylmercury and effects of PCBs
19 in the sensory system, motor function, and cognitive
20 deficits, but at this time it's not possible to
21 differentiate the effects of PCBs and neurodevelopment

1 from effects of methylmercury in experimental animals
2 mostly because of the lack of mechanistic information.

3 We have to keep in mind that in this situation, we
4 have a very rich data set, at least for us who do
5 environmental kind of exposures think it's rich, and
6 it's extraordinarily rich regarding exposure and
7 extraordinarily rich regarding response. What we don't
8 know is what's happening in between in terms of the
9 critical cellular steps that may be involved in
10 producing the neurological effects that may be seen,
11 the migration of critical neurons and so forth, and
12 that's an area of research that would yield great
13 benefit to the public health assessments of both
14 methylmercury and PCBs.

15 There are five panel recommendations and findings
16 that emerged out of the workshop, and I'll go through
17 them one by one. Again, this was agreed upon by all
18 the participating agencies, the panel, and also the
19 major study groups out of the Seychelles and the
20 Faroes.

21 1. Methylmercury is a developmental neurotoxin,

1 but effects -- We still got the same sentence in here -
2 - at low does encountered by eating fish are difficult
3 to evaluate. Not too much progress there, but
4 certainly a strengthening of that statement.

5 2. All the studies reviewed were considered of
6 high scientific quality and the panel recognized that
7 each of the investigators had overcome significant
8 obstacles to produce important scientific information.

9 That was uniformly felt throughout the panels. We
10 felt that a continued funding of these studies is
11 necessary for the full potential to be realized. It's
12 particularly true for the Faroes and Seychelles, which
13 are currently assessing developmental effects of
14 methylmercury in the fish-eating populations, of
15 course. The developmental studies would benefit by
16 evaluation of common endpoints using similar analytical
17 methods. And we noted that the Amazon study, although
18 positive results were seen, did not look at
19 developmental endpoints. A later study out of
20 Grandjean's group that's just been published has looked
21 at the Amazon studies where methylmercury exposure

1 occurred through gold mining, and those results were
2 positive as well in terms of visual-evoked potentials
3 and some other measures of neurological function,
4 following prenatal as well as post-natal exposure.

5 3. Results from the Faroes and Seychelles
6 studies are credible and provide valuable insights into
7 the potential health effects of methylmercury.

8 4. Some differences are clearly present in the
9 results of the studies, but the panel was unable to
10 clearly identify the sources of these differences.
11 Among possible sources are the different effects of --
12 Again, coming back to this one -- episodic versus
13 continuous exposure, ethnic differences, a lack of
14 common endpoints in the Faroes and Seychelles studies -
15 - A very important one, of course -- and several other
16 confounders or modifying factors such as those found in
17 the diet, lifestyle, as well as chemicals present in
18 seafood, which is a source of methylmercury to these
19 populations.

20 The other chemical constituents that may be
21 explanatory include those that may be beneficial to

1 fetal development, like the omega-3 fatty acids, and
2 those that may be harmful to fetal neurodevelopment,
3 such as the PCBs.

4 5. These studies have provided valuable new
5 information on the potential health effects of
6 methylmercury, but significant uncertainties remain
7 because of issues related to exposure, neurobehavioral
8 endpoints, confounders and statistics, and design.

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

12 There has been a few publications I mentioned that
13 have come out since we've had the report, and maybe Tom
14 Clarkson will give us an update of what's going on with
15 his group as well in terms of recent publications.

16 These are mostly from the Grandjean group and they
17 involve the one shown here in terms of the Amazon
18 study, which I mentioned; a paper -- another paper from
19 the Faroe Islands on the delayed evoked potentials in
20 children exposed to methylmercury from seafood; a paper
21 with Murata as the first author and Grandjean the last,

1 evoked potentials in Faroese children prenatally
2 exposed to methylmercury; and another one that examined
3 hypertension, a reported increase in hypertension in
4 the kids exposed to methylmercury, also in the Faroe
5 Islands. This paper, I believe, now is in press. It
6 was presented at that Rio De Janeiro meeting in May of
7 this year.

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

11 Now, I'll make a few points here that I think most
12 of them have already been made, maybe some of them
13 haven't, regarding ethylmercury and possible
14 comparisons with methylmercury.

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

1
2 This dose of mercury on vaccination day is much
3 higher than daily exposure in the Seychelles and the
4 Faroes, although the total dose received from vaccines
5 is less than the mean exposures in the Faroes and
6 Seychelles. Infant mercury intake per day from dietary
7 sources is estimated to average .05 micrograms per
8 kilogram per day in a chronic exposure; and this would
9 be primarily through lactation as well as some other
10 sources. And there's a few pieces of information in
11 the scientific literature that support that estimate of
12 infant uptake of methylmercury, exposure to
13 methylmercury.

14 Biological half-life, similar to methylmercury.
15 This is a little bit different than what was said this
16 morning. For methylmercury, it's 40 to 150 days, and
17 this was based on a number of different studies that
18 have been presented. I think different agencies use
19 slightly different numbers, but I think the average --
20 Chris, would it be right, it's about 70 -- 60 or 70, in
21 that range? The one study I got ahold of regarding

1 thimerosal, or ethylmercury, came from a suicide
2 attempt. This was published three years ago actually,
3 in "Clinical Toxicology," and this one lived. He also
4 got about 80 milligrams per kilogram of thimerosal, and
5 the half-life -- and Chris (inaudible) had sent me this
6 reprint on Friday. It was estimated that the half-
7 life, the second phase of the half-life, which is the
8 one we need to look at here, was roughly 40 days in
9 this one individual who survived that episode. Of
10 course, we don't know what a near-death experience does
11 in terms of the physiological factors that govern half-
12 life, so I wouldn't guarantee that that's the half-
13 life.

14 The information that we have in total suggests
15 that it might be slightly shorter than methylmercury.
16 And there is really no definitive information on
17 potential differences that I could uncover between
18 infants, children, or adults regarding biological half-
19 life. I don't know, Katie, if you have some more
20 information on that.

21 Metabolism -- And I think this was brought out in

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

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

18 A second study, which was not discussed this
19 morning, is that adult male and female rats were
20 administered five daily doses of equimolar
21 concentrations of ethyl or methylmercury by gavage and

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

13 And after having said that, there are a number of
14 critical toxicology studies that could be conducted to
15 address some of the uncertainties that -- and you
16 probably all know about and we talked about this
17 morning. Unfortunately, all of these take time and,
18 you know, clearly, if we embarked upon these studies
19 now, we're not going to have results until long after
20 some of the initial and significant decisions have to
21 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
7 those response and age dependent responses in
8 appropriate systems. We need to, for the reasons I
9 discussed earlier regarding the PCBs and methylmercury,
10 look at mechanistic studies, and we need to focus on
11 critical changes in gene function and cellular
12 pathways. In all the toxicology studies we do in the
13 national toxicology program, and we do 30 or 40 of
14 these a year as part of that interagency program, we're
15 starting to take increasing advantage of the human
16 genome project and what that allows us to do in terms
17 of looking at patterns of gene expression following
18 exposure to various toxicants to compare potency of
19 different agents and also mechanism of action, as one
20 agent going through a similar mechanism of action as
21 another agent. That might be particularly relevant to

1 the issues at hand for the ethyl/methyl issue.

2 Evaluation of possible sensitive subpopulations
3 based on either genetic predisposition, diet, or
4 cumulative risk. Again, we're exposed to other
5 developmental neurotoxicants. Are they additive? Are
6 they synergistic? Are they antagonistic towards each
7 other? Do they block each other's effect? And
8 biomarkers of exposure, including hair, need to be
9 evaluated.

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

16 I couldn't help but to show a couple of slides
17 here. One of the things that I do in my own laboratory
18 is work with biomathematicians to develop
19 physiologically-based pharmacokinetic models, and this
20 is a model that might be applied to a prenatal
21 methylmercury study. When you have various kinds of

1 compartments in the maternal system and also the fetal
2 system, looking at placental transfer. Of course,
3 excretion in the maternal system, either through the
4 urine or the feces. Blood levels, relationship to hair
5 levels, secretion in the milk, of course, when you're
6 looking at lactational exposure post-natally.

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

16 So I think these kinds of models are always very
17 helpful in health assessments. And I know agencies
18 such as EPA, ATSDR, and FDA use them extensively in the
19 health assessments that they make. But in the case of
20 the vaccine issue, we really have to look at it in
21 terms of the infants and children issue, which we've

1 discussed already, and I think the point has been made
2 that we have information in adults, we have information
3 in effects on prenatal development, and we have very
4 little information about the relative sensitivity of
5 infants, either to adults or to the developing fetus.
6 So we need to develop that type of physiological-based
7 pharmacokinetic model, to look particularly at the
8 issue of infants and children and how tissue
9 concentrations might be related to the potential for
10 adverse health effects.

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

18 So you collect the data, refine the model, compare
19 it to the existing knowledge base. You start circling
20 through this thing a few times. By the time you get
21 through it a few times, you're then in a position to

1 use it in dose response assessment and quantitative --
2 other aspects of quantitative risk assessment, but,
3 again, these things take time. We're not going to both
4 generate the data and generate these types of models,
5 you know, within the next six months. It's going to
6 take some time to do that.

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

16 (LAUGHTER)

17 **DR. LUCIER:** But, you know, some of my favorite,
18 of course, are molecular biologists, you know, you're
19 stupid, I'm smart. I actually know a lot of molecular
20 biologists that aren't smart.

21 (LAUGHTER)

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

4 Regulatory official, that's definitely not true in
5 this room. I tell you, the interagency group that I
6 worked with in this was absolutely terrific. But one
7 caricature would be, "Don't trouble me with science."

8 Industry, "Positive results are meaningless." And
9 environmental activists, "If it's chemical, it's bad."

10 Lawyer, do we have any lawyers here?

11 (LAUGHTER)

12 **DR. LUCIER:** I heard a joke about lawyers the
13 other day, that 99 percent of the lawyers give the
14 other 1 percent a bad name.

15 (LAUGHTER)

16 **DR. LUCIER:** And as a result of all this,
17 frequently the public health decisions that come out of
18 the federal government, because of these various
19 caricatures, really aren't believed and the public
20 doesn't trust us. So I feel very good about this
21 workshop because, I think, as was stated in the

1 original goals that the purpose, to get all the
2 information out on the table, what we know and what we
3 don't know, do it in an open context where people can
4 comment, add to it, subtract from it, and so forth, I
5 really think is the way to go about this.

6 So I appreciate the invitation and the opportunity
7 to participate. Thank you.

8 (APPLAUSE)

9 **DR. GREENBERG:** Thank you, George. We have some
10 time for some questions. Too much data for you, huh?
11 Dixie?

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

13 You indicated that the mechanism by which
14 methylmercury might be exerting its neurotoxic effects
15 is unknown. Are there any reasonable hypotheses in
16 your mind? And how would that relate to ethylmercury
17 and methylmercury with regard to mechanism?

18 **DR. LUCIER:** You know, there's some information
19 available -- And, again, I'm not a neurochemist or a
20 neurotoxicologist, so maybe some of the other folks who
21 have looked at this on the panel could add to my

1 answer. But there have been effects shown on various
2 constituents that are involved in their own migration
3 and other aspects of neurodevelopment. I don't think
4 there's anything that people would say, "Aha, I think I
5 understand what that critical event is that's producing
6 the toxicity."

7 You don't have to know all the steps that are
8 involved, but what you really want to know is what the
9 key critical event is or the mode of action is, and
10 once you have that information, you're on much better
11 footing in which to compare and predict responses that
12 might be occurring across the chemical class.

13 Say, for example, it was done with the
14 environmental estrogens or the dioxins where we knew
15 the mode of action was receptor mediated -- Let me talk
16 about something I know something
17 about -- we're then able to take classes of chemicals
18 and see how well they interacted with that system and
19 produced a specter of deemed changes that are
20 associated with it and use that information in
21 regulatory decision-making in terms of determining

1 which of these dioxin analogues or which of these
2 environmental estrogens are the ones we need to be
3 worried about.

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

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

8 DR. RABINOVICH: You stated -- And I'm questioning
9 this because I'm not sure I understand it or if anybody
10 else in the room does also. You stated that the
11 demethylation of methylmercury appears to occur more
12 slowly than the deethylation of ethylmercury.

13 Can you expand on the implications of that? Is
14 that good or is that bad?

15 DR. LUCIER: Well, you know, I wish -- I'd like to
16 say I knew, but I've heard that it's good and I've
17 heard that it's bad.

18 (LAUGHTER)

19 DR. LUCIER: I've heard that it's good because
20 this is a detoxication step in some respect. Say, in
21 terms of the kidney, it's a way of, you know, getting

1 the mercury out of the body. And I've also heard --
2 But since we don't know how methylmercury works, we're
3 at a little bit of a loss to make too much of a
4 definitive statement. I've heard from others that
5 maybe it creates a mechanism for retention of mercury
6 in the brain as the inorganic mercury is then -- does
7 not retrograde cross the blood/brain barrier. So it's
8 a mechanism retaining mercury in the brain.

9 So, I don't know. I think it's a real finding . .
10 . and I think it's an important finding, but I don't
11 know how to quite put it in the context of the
12 comparative toxicity issue.

13 I think it is important to note from the Magos
14 study, in which he directly compared ethyl and
15 methylmercury, that he found essentially the same
16 results in both studies, with the exception that the
17 renal toxicity was greater with ethyl, and I think that
18 was because of the demethylation as a way of
19 concentrating the mercuric chloride or inorganic
20 mercury in the kidney.

21 **DR. RABINOVICH:** Okay.

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

3 In analyzing the Faroe Island data, which are the
4 positive set of data, in thinking about -- at least in
5 thinking about microbiology, one can usually calculate
6 a 50 percent dose, that is, to say a dose that caused a
7 reproducible effect 50 percent of the time.

8 Now, from my reading of the Faroe Island studies,
9 there is no level in those studies that had a 50
10 percent effect, but there are mathematical ways of
11 trying to predict the 50 percent effect.

12 So my question, if it is a question, is: Can you
13 calculate from the Faroe Island study what is the 50
14 percent effective dose, either in terms of hair level
15 or blood level of mercury?

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

20 The Faroes data doesn't have adequate information
21 within it to define a slope down in that low-dose

1 region. Now, in the absence of that type of data, one
2 can use various types of models to extrapolate to an
3 EC-50 concentration using some of the parameters
4 already looked at. Several assumptions would have to
5 be made, but my guess is any extrapolation of that
6 nature, because of the nature of the data set, would be
7 highly subject to debate and criticism because of the
8 assumptions that would have to be made:

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

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

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

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

16 You mentioned that we don't understand the
17 mechanism by which the neurotoxicity occurs, and we
18 also don't know what the relative sensitivity of the
19 infant is, which is what we are all concerned about
20 right now.

21 I'm wondering if there's any information that

1 might be applicable or might help educate us with
2 regard to the slope of the curve for other
3 developmental neurotoxins. There's lead, there are
4 others. We -- I don't think this audience knows what
5 those slopes look like, and whether you think they may
6 be at least informative. You can't necessarily apply
7 them directly to mercury, but it would help to try to
8 get some estimate of what the relative increase in
9 toxicity for an infant is at birth, at two months, as
10 compared to at six months or at twelve months.

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

13 **DR. LUCIER:** Yeah. That's -- I think that's a
14 great point, and I'm not a neurotoxicologist again, so
15 I don't have that information at hand. We have --
16 We've analyzed through the NTP a lot of chemicals in
17 our neurotoxicology batteries. So maybe it would be
18 worthwhile for me to go back and ask those folks to
19 look at that particular issue and see what comes out of
20 it.

21 And many of these, of course, are assumed to have

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

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

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

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

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

14 Looking at inorganic lead, you can get an
15 interesting comparison because the occupational levels
16 that are considered acceptable are more in the range of
17 40 and 50 micrograms per deciliter, with reproductive
18 effects certainly at lower levels.

19 There's also a body of literature showing sort of
20 neuropsychological changes at around 25 to maybe 40
21 micrograms per deciliter as a blood level. For the

1 infant and young child, the levels which effects are
2 found are certainly less than 10 micrograms per
3 deciliter, with some studies finding effects below 10.
4

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

17 So I think it's kind of roughly in that range, but
18 it's really the type of effect you're looking at and,
19 certainly, a lot of variability within individuals.

20 **DR. RABINOVICH:** I guess to follow-up one question
21 to either of you -- I'm Gina Rabinovich, NIAID -- Is it

1 appropriate at this point in the discussion to be using
2 the word "mercury" versus methyl or ethyl? Do we
3 accept that methyl is the appropriate model for what's
4 going on in the infant? And you were talking about
5 mercury. Is that relevant, you think, to both?

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

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

1 differently.

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

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

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

1 Because --

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

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

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

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

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

20 **DR. LUCIER:** I wouldn't fully agree. I would say
21 the limited data that's available does not justify

1 anything else but assuming that they're similar. But I
2 -- So I basically agree with it, but not fully.

3 DR. GREENBERG: We have time for one or two more
4 questions.

5 DR. MYERS: Martin Myers, NVPO.

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

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

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

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

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

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

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

19 Now, some very interesting questions come up.
20 Only methylmercury gets into hair. Inorganic doesn't
21 very well. So whether ethylmercury gets into hair is a

1 very interesting question. It probably does based on
2 the chemistry of the thing -- You know, they look very
3 similar in their behavior -- but we have not -- we will
4 now. We will now check the hair samples to see if
5 there's any ethylmercury in there.

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

8 (LAUGHTER)

9 DR. LUCIER: But your -- That's a good question,
10 Martin, and the answer is, yes, we have to think about
11 the vaccine exposure in addition to the exposures that
12 are already occurring.

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

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

20 DR. GREENBERG: It is.

21 DR. CLARKSON: Bear in mind that the average level

1 in the Seychelles in hair is about, let's say, seven
2 parts per million, which roughly corresponds to a blood
3 level of about 30 parts per billion. Okay. That's the
4 average. So the calculations I showed you this
5 morning, which were very extreme calculations assuming
6 a very small bodyweight and assuming they got the full
7 three or four doses of vaccines, you know, the blood
8 level might get up to 20. But you saw the -- The
9 published figures I think were quoted from the Emory
10 study of about 7, as I remember, 7 parts per billion.

11 So certainly it could make a contribution.
12 There's no doubt it could make a -- it wouldn't be an
13 overwhelming one, but it would be a contribution.

14 **DR. GREENBERG:** Maybe I misunderstood. I got
15 somewhere between 20 percent and 60 percent of blood
16 level from what you just said.

17 **DR. LUCIER:** But I think you have to go back and -
18 - I think that the age at which these assessments are
19 being done, in the last case, in Dr. Clarkson's study,
20 of 66 months of age, and the Faroes is 84, so there's
21 been a lot of half-lives that have elapsed since the

1 vaccination had occurred.

2 DR. CLARKSON: The interesting point about -- you
3 raised, though, about -- I mean, you're talking about,
4 of course, post-natal exposure, now, from the vaccines
5 -- Right?

6 DR. GREENBERG: Yes.

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

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

1 DR. GREENBERG: One last question.

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

5 I presume some babies at both of these sites are
6 breast-fed and some babies are not breast-fed, and I
7 guess I'm wondering about -- And this is an
8 immunization practice question -- do very young infants
9 eat fish there? Do they eat this whale meat, blubber
10 and things, because they certainly don't eat -- very
11 young children don't eat fish in this country very
12 often. So I wonder about the magnitude of the
13 exposure, whether you expect there to be a difference
14 given your proposed route of exposure, breast-fed
15 versus not breast-fed.

16 DR. LUCIER: I wouldn't expect that they do, but I
17 don't know that for sure. Does anyone -- Can anyone
18 comment on that, regarding the -- particularly the
19 Faroes study? I wouldn't expect that they'd be eating
20 many meals of homogenized pilot whale meat.

21 DR. GREENBERG: I'm going to have to end this very

1 interesting discussion now because --

2 (LAUGHTER)

3 **DR. GREENBERG:** -- I'm getting sick to my stomach.

4 The next speaker is Dr. William Raub, who is the
5 Deputy Assistant Secretary for Science and Policy in
6 the Office of the Assistant Secretary for Planning and
7 Evaluation, HHS, and the title of his talk is
8 "Guidelines for Safe Levels of Exposure.

9 **DR. RAUB:** Thank you very much, and I appreciate
10 the opportunity to join you this afternoon. The format
11 for the next hour, or a little bit less, is that I will
12 make some introductory remarks around the health
13 guidance values, and then I will be joined by a set of
14 colleagues, including Dr. Clarkson, as a panel
15 discussion, and they have promised to answer every
16 question that I manage to raise.

17 We've heard repeated references or questions to
18 the health guidance values this morning and issues
19 around whether to use them, and if so, when and how to
20 use them. I believe we will be able to do more to
21 raise issues than to give sharp definitive information

1 around some of those questions, but I thought it might
2 be helpful to have some of the background around what
3 these concepts are, what's the philosophy, and the
4 generic approach to them.

5 All of these guidelines attempt to focus on a
6 concept for which I made up a neutral name, the "Safe
7 Daily Exposure." The emphasis is on long- term. The
8 emphasis is generally is on very low levels of
9 exposure. The usual units are the quantity per unit of
10 bodyweight per unit of time. And, for example, for
11 mercury in its various forms, methylmercury, in
12 particular, micrograms per kilogram of bodyweight per
13 day.

14 These health guidance values are calculated
15 individually for many different hazards, depending on
16 the regulatory or other mission of the agency that's
17 involved. They are calculated specifically for various
18 primary routes of exposure, ingestion, inhalation, or
19 dermal exposure. In general, they are projected either
20 as a lifetime value or, more conservatively, at the
21 very least, for some substantial indefinite period.

1 The three most common of these health guidance
2 values are the reference dose, or RfD, of the U.S.
3 Environmental Protection Agency; the minimum of risk
4 level, or MRL, of the Agency for Toxic Substances and
5 Disease Registry of the Department of Health and Human
6 Services; or the acceptable daily intake, or the ADI,
7 employed by the Food and Drug Administration.

8 Algebraically, these are essentially the same
9 thing. They are used depending on the mission of the
10 various agencies. They may be used as the starting
11 point for health assessments in such situations as
12 evaluating the risks presented by a superfund site.
13 They may be used in a formal risk assessment of a
14 particular hazard, including all of its distributional
15 phenomena and the like. They may be used as a
16 starting point for developing regulatory requirements
17 for emissions in the air or water, for assessing the
18 toxic levels in particular situations, or, in the FDA's
19 case, for the regulation of commercial seafood. But,
20 again, the common factor is the notion that these are
21 starting points for those more specific assessments and

1 applications, and in virtually no case is the guidance
2 value considered the last word. It's usually
3 considered the place to begin in terms of a specific
4 use.

5 In all of this, there is a driving desire to have
6 science-based values to the extent possible. And in
7 its simplest form, the algebra comes down to the notion
8 of the safe daily exposure being a ratio of an
9 estimated gleaned from real data, either experimental
10 data on animals or epidemiologic observations with
11 humans, divided by one or more uncertainty factors.

12 And what this says is the science-based goal here
13 involves two aspects of science. One is actual data,
14 experimental or observed, and the other are informed
15 judgments as to the utility of that data, the
16 limitations of it, and the ways in which it might be
17 applied, and that's everything from the selection from
18 the particular studies from which to fill the numerator
19 to the judgment about the number and size and the
20 rationale for the uncertainty factors that constitute
21 the denominator.

1 Certain priorities obtained in general with
2 respect to how one chooses that numerator term. Other
3 things being equal, there's a clear preference for the
4 -- what is called from the direct data, the "no
5 observed adverse effect level," or the NOAEL. If
6 there's dose response information available, and one
7 can indeed identify the level, usually the highest
8 level at which no adverse effect is seen, then this is
9 often an excellent beginning for this calculation.

10 More often than not, we find ourselves faced not
11 with the "no adverse effect" level but rather observing
12 adverse effects in many different levels and,
13 therefore, being forced to choose the lowest observed
14 adverse effect level. This has a bearing then on what
15 uncertainty factor is chosen, because having seen the
16 lowest observed one, one may have no certain
17 information or no good basis to predict where the level
18 of no effect actually is.

19 Another priority judgment around the selection of
20 that numerator term is the type of information on which
21 the experimental or observational data are based.