

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

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

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

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

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

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

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

1 **DR. GREENBERG:** Thank you, Dr. Englhardt.

2 (APPLAUSE)

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

5 **DR. KIM:** Dr. Kim, from Los Angeles. You provided
6 data, I think, primarily in adults. Are there any data
7 available in either experimental animals and inputing
8 rodents and monkeys, primarily looking to the tissue
9 distribution and metabolism in babies, neonates?

10 **DR. ENGLHARDT:** No, there's no neonatal data that I've
11 been able to uncover. The last article for an animal
12 study that I was found was that 1976 article by Blair.

13 I have not been able to uncover anything in terms of
14 new studies that have been published. We did have one
15 unpublished report on the teratology study, but nothing
16 in terms of postnatal development or exposure in the
17 neonate.

18 **DR. KIM:** It seems you indicated that mercury compound
19 crosses the blood/brain barrier and the placenta
20 barrier. I guess at this juncture it is unknown
21 whether the exposure of a single dose or chronic doses
22 may have a deleterious effects on the

1 neurodevelopmental aspects?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

10 (NO RESPONSE WAS HEARD)

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

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

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

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

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

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

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

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

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

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

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

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

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

16 I put this slide up to remind us that life was simpler
17 not too long ago. This schedule was taken from the
18 1988 Red Book -- This was when I was a pediatric
19 resident -- and it demonstrated that during the first
20 six months of life, infants only received five vaccines
21 and only three of which, the DTP, contained thimerosal.

22 The HIB vaccine here at this time was recommended at

1 the eighteen-month visit.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

10 It's important to remember that here
11 that's -- you see that most of the reports involve local
12 hypersensitivity reactions. The most common vaccine
13 that was identified was hepatitis B. And it's
14 important to realize the limitations of this data.
15 Causality cannot be inferred both because of the
16 passive nature of VAERS and the many antigens present
17 in vaccines in addition to thimerosal.
18 Because of this lack of data on low-dose thimerosal
19 toxicity, we made the conservative assumption, and
20 perhaps controversial assumption as we'll hear and
21 we've heard already, that ethylmercury toxicity was
22 analogous to methylmercury toxicity. Since thimerosal

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

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

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

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

1 kilogram per day.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 products.

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

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

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

21 (APPLAUSE)

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

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

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

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

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

10 **DR. PLOTKIN:** Yes.

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

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

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

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

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

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

20 **DR. BALL:** Right.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 for projecting this?

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

3 Thank you.

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

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

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

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

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

22 (LAUGHTER)

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

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

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

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

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

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

1 **DR. GREENBERG:** Thank you.

2 Do we have other questions?

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

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

19 **DR. GREENBERG:** Dixie?

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

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

4 DR. BALL: Exactly.

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

7 DR. BALL: Methylmercury.

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

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

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

12 DR. BALL: Right.

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

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

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

18 DR. BALL: Yes.

19 DR. SNIDER: -- ethylmercury to methylmercury?

20 DR. BALL: Ethylmercury to methylmercury.

21 DR. SNIDER: In micrograms?

22 DR. BALL: In micrograms.

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

2 DR. BALL: Right.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

14 **DR. BALL:** Correct.

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

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

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

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

6 **UNIDENTIFIED SPEAKER:** Yes.

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

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

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

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

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

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

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

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

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

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

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

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

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

1 who did a great job.

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

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

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

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

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

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

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

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

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

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

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

1 this morning.

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

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

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

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

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

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

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

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

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

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

1 have much for infants.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 nervous system.

2 Third, exposure response relationships were based on
3 surrogate markers and hair or blood concentrations in
4 fetal and children's brains can only be estimated.

5 While this is true, I think for the reasons that I've
6 said before, I think we have a wealth of information
7 about exposure and what it means in terms of hair
8 levels, not that we can't get more, but I think that
9 information was pretty good. It was not considered a
10 major problem or a major reason by the panelists for
11 the different results between the Faroes and the
12 Seychelles.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

12 What about the toxicity of ethylmercury or thimerosal?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 take some time to do that.

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

11 (LAUGHTER)

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

16 (LAUGHTER)

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

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

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

5 (LAUGHTER)

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

9 (LAUGHTER)

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

1 (APPLAUSE)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

9 (LAUGHTER)

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

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

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

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

10 **DR. RABINOVICH:** Okay.

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

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

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

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

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

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

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

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

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

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

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

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

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

9 There's lead, there are others. We -- I don't think
10 this audience knows what those slopes look like, and
11 whether you think they may be at least informative.
12 You can't necessarily apply them directly to mercury,
13 but it would help to try to get some estimate of what
14 the relative increase in toxicity for an infant is at
15 birth, at two months, as compared to at six months or
16 at twelve months.

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

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

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

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

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

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

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

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

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

1 certainly at lower levels.

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

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

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

1 certainly, a lot of variability within individuals.

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

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

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

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

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

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

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

1 Because --

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3 (LAUGHTER)

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

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

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

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

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

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

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

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

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

21 **DR. GREENBERG:** Yes.

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

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

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

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

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

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

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

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

15 (LAUGHTER)

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

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

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

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

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

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

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

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

19 Algebraically, these are essentially the same thing.
20 They are used depending on the mission of the various
21 agencies. They may be used as the starting point for
22 health assessments in such situations as evaluating the

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

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

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

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

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

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

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

16 Failing that, data from non-human primates are
17 obviously desirable, and failing that, data from other
18 mammals.

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

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

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

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

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

3 If two or more uncertainty factors are employed, in my
4 experience, more often than not, they're multiplied.
5 But, in certain circumstances, if there is some
6 mechanistic information, one might choose to do an
7 additive of those instead. Again, there may be no
8 right answers with any complete determination, but
9 informed judgments as to how best to weigh the quality
10 and relevance of the information to the task at hand.
11 And finally, these are some, and only some, of the
12 characteristics that affect these health guidance
13 values. A number of my colleagues who will be speaking
14 to you in a few minutes could give a week-long seminar
15 on the intricacies of the assumptions and the
16 calculations that go into these determinations. But,
17 in general, these focus on chronic exposure, seeking
18 that long-term, potentially lifetime level that is
19 judged to be safe.

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

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

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

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

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

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

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

5 Kate, would you like to start us off?

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

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

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

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

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

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

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

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

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

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

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

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

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

1 appropriate to adopt.

2 That's the extent of my comments.

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

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

7 Chris DeRosa?

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

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

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

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

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

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

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

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

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