

1 we need to modify in any way, that would be very
2 helpful.

3 Some of the issues that I think were germane to the
4 discussions that we had you've heard a lot about, and
5 that is the assumption about ethylmercury being treated
6 as methylmercury. I think that that's still the
7 appropriate thing to do. I haven't heard anything at
8 this workshop that suggests that we don't need to do
9 that.

10 Another assumption was that the fetal risk, which is
11 what guidelines are based -- are trying to address, was
12 equal to infant risk, I think we are hearing that
13 perhaps infant risk is lower than fetal risk. So
14 that's a reassuring thing. It's not that we have a lot
15 more data on this, but it's tending to go in the
16 direction from what I'm hearing that infant risk post-
17 natally may be lower than fetal risk. No one is quite
18 ready to make a new guideline I don't think, but it's
19 reassuring rather than being more -- becoming more
20 worrisome.

21 On the issue of the background level of exposure to

1 mercury, the assumption was made that it's negligible,
2 and I haven't heard anything that makes us believe that
3 we ought to be more concerned about background levels
4 of exposure.

5 Another important issue that has permeated these
6 discussions is that the guidelines are based on chronic
7 exposures. What we are dealing with is an acute
8 exposure and the guidelines may not be applicable. I
9 think, on that score, it still remains unknown. I've
10 heard data on both sides, or observations, I should
11 say, or speculation on both sides, and in my mind this
12 still remains an unknown.

13 In the Department of Health and Human Services, there
14 were three guidelines. I think it's fair to say that
15 because of a two-year process that has been going on in
16 the Department of Health and Human Services, while
17 there were three existing guidelines in the U.S. more
18 weight or preference was given to the ATSDR guideline
19 as the primary guideline to be -- to be guided by, if
20 you will, than the other two. That was a decision that
21 was made, as I say, in the Department of Health and

1 Human Services because of a two-year process. I've
2 heard nothing to make us believe that we ought to have
3 done that any differently.

4 Also, another point that arose during the whole
5 discussion was how do you apply these guidelines in
6 decision-making. I've tried to allude to that by the
7 schematic that I showed on the safety margins, but this
8 was a big issue. Again, depending on how you interpret
9 those guidelines, as either bright lines or as starting
10 points, can make a big difference in how you react to
11 all this, and I think -- I haven't heard anything to
12 change our view, which was to look at these guidelines
13 as a starting point.

14 In fact, the more I've heard about this, the more I've
15 become convinced that -- at least in Dr. Raub's session
16 yesterday, there was a lot of focus on the guidelines
17 as screening points or screening levels.

18 And, finally, I don't have a slide for this, but I'd
19 like to talk about some of the issues that have arisen
20 that I'm aware of in the implementation of the existing
21 policies.

1 One of them obviously has to do with hepatitis B. I
2 mean, that's the only vaccine where we expressed a
3 change in the current status. You heard Dr. Mast's
4 presentation yesterday, concerns being raised about the
5 number of infections that may be arising as a result of
6 the new policy change. Perhaps that's something that
7 we were not as fully aware of and didn't have all those
8 calculations at the time the policy was made. The
9 question is, do we need to revisit that in some way?
10 The workability of having an age range, we said that
11 the AAP and the PHS recommend from age two to six
12 months. What is the workability of this? How much
13 difficulty is this causing in the field in terms of
14 confusion among different groups.
15 I think we thought when we issued the recommendation
16 that it would be workable. My impression is that it is
17 working, not without bumps in the road, but that it is
18 a workable recommendation.
19 One other area has to do with communication, and
20 perhaps we need to look at improving communication with
21 providers and parents about this change. We heard from

1 a speaker in the audience from Philadelphia about
2 confusion that is being caused, and even some mothers
3 of infants of antigen-positive mothers may not be
4 getting vaccine. That clearly is not a change. There
5 has been no change for antigen-positive mothers, and
6 maybe in the communication arena something needs to be
7 revisited.

8 Vaccine supply issues. Issues have arisen about how to
9 manage the stocks of thimerosal-containing and non-
10 thimerosal-containing vaccines. There are issues about
11 what's in the pipeline and what's going to happen to
12 the stocks of vaccine. This may be an issue that we
13 need to visit that we haven't fully addressed.

14 Another one has to do with the supply of vaccines. We
15 may, in the near future, have greater availability of
16 thimerosal-free vaccines. If that happens, will we
17 want to express any preference for thimerosal-free
18 vaccines as they become available? If they're only
19 available from one or some manufacturers but not
20 others, this has implications for the long-term supply
21 of vaccines. Do we want to address that in any way?

1 And, fourthly, there are issues around flu vaccination.

2 You've heard there have been no recommendations yet.
3 I think that's in the works and, perhaps, not something
4 that we need to be overly concerned with. That will
5 take place.

6 And finally, there are issues around research and a lot
7 of unmet needs in the information area, and that will
8 be the subject of Dr. Rabinovich's panel following
9 later in the morning.

10 So I hope my presentation does provoke some additional
11 discussion about both the issues that were behind the
12 policy discussions, as well as some of the issues that
13 have arisen in implementation.

14 Thank you very much.

15 (APPLAUSE)

16 **DR. MODLIN:** Thanks, Roger.

17 In the interest of time, I'm going to ask we not take
18 questions, and then I'll -- but I'm certainly going to
19 ask Roger to join the panel up here at the end, and I'm
20 almost certain that we will have a fair amount of time
21 for discussion and questions at that time. So we'll

1 ask some of our other -- the other presenters to go
2 next.

3 And the first presentation will be by Dr. Jon Abramson.

4 Dr. Abramson is Professor and Chair of the Department
5 of Pediatrics at Bowman Gray School of Medicine. He is
6 the new -- the brand-new Chair of the Committee on
7 Infectious Diseases of the American Academy of
8 Pediatrics, which, of course, has been out front, if
9 not antagonistic (sic), on this issue.

10 So we're happy to have Jon here. Thanks.

11 **DR. ABRAMSON:** Thank you, John.

12 I think I have to tell a story. It's actually a joke,
13 but you'll understand the moral at the end.

14 There was a millionaire in Florida who put an ad in the
15 paper and said, "I'll give a million dollars, a yacht,
16 or my daughter's hand in marriage to anybody who can
17 swim one lap in my pool."

18 The next morning there were 50 people out by the pool.

19 Everybody was standing around. The millionaire comes
20 out, thanks them for coming, and then he says, "The
21 only thing I haven't told you is there are 12

1 alligators in the pool." And everybody's standing
2 around buzzing and saying, you know, "This isn't worth
3 it. It's not worth dying over."

4 All of a sudden there's a splash in the pool, and the
5 alligators converge, and guy dives down, comes up about
6 halfway, the alligators converge, he dives down and
7 comes up. And he's pulling himself out of the pool,
8 the alligator bites him on the leg, and he's lying on
9 the pool bleeding, and the millionaire comes up to him
10 and says, "That's the bravest thing I've ever seen."

11 He said, "I assume you want the million dollars."

12 "No."

13 He says, "I assume you want my yacht."

14 "No."

15 He says, "Then you want my daughter's hand in
16 marriage?"

17 He says, "No, I don't even know your daughter."

18 So he says, "What do you want?"

19 He says, "I want the person who pushed me in the pool."

20 (LAUGHTER)

21 **DR. ABRAMSON:** Well, it was an interesting conversion

1 over to -- taking over -- from sitting on the committee
2 to actually being the Chair.

3 (LAUGHTER)

4 **DR. ABRAMSON:** And I'd like to highlight a few of the
5 issues. I think there was major areas of agreement.
6 In fact, I think for the Public Health Service and the
7 American Academy of Pediatrics the vast majority of
8 issues were agreed upon.

9 Number one, we all agreed that the risk of not
10 vaccinating children for every one of the 11 diseases
11 that we try to prevent with vaccines far outweighed any
12 potential risk of giving the vaccine containing
13 mercury.

14 Two, that we should eliminate or reduce as quickly as
15 possible the amount of mercury in vaccines.

16 And three, which hasn't really been pointed out this
17 morning, is that we agreed that we should delay the use
18 of the vaccine in the baby who is born at term and not
19 use it at term. And why is that? And the reason is
20 that even if you take a full-term baby who weighs 3
21 kilograms and you take any of the standards, from the

1 EPA standards to the FDA standards, you are exceeding
2 on that day the amount of mercury that is -- that
3 guidelines recommend you give, by greater than tenfold.

4 And we don't know what the safety margin is. This was
5 pointed out today, and I'm sure it was pointed out
6 yesterday, we don't really know whether it's cumulative
7 dose or what that really matters. So we both -- Both
8 the Public Health Service and the American Academy of
9 Pediatrics agreed that the hepatitis B vaccine should
10 be delayed in a mom who is hepatitis B surface antigen
11 negative.

12 So what were the two areas of divergence? And I must
13 state up front that some of the confusion that has
14 occurred has been because of the areas of divergence.
15 We certainly get letters at the Academy asking us why
16 we diverged, and at some point, we probably need to
17 write an editorial just talking about the whole process
18 that went on. Because one of the issues that I'm going
19 to raise later on is: How do you deal with emergencies
20 when the approval process for recommendations varies
21 substantially between the American Academy of

1 Pediatrics? How do we go through the process of
2 getting our recommendations approved? We, as a
3 technical committee, the Committee on Infection Disease
4 goes through the process of getting our recommendations
5 approves, versus the ACIP or any part of the Public
6 Health System which has to go through a very different
7 process.

8 So where did we diverge? We diverged a little bit at
9 when should you start the hepatitis B vaccine, and it
10 simply was over a matter of how safe do you want to be.

11 Everything we did with hepatitis B and the hepatitis B
12 surface-antigen-negative mom related to how safe do you
13 want to be, what kind of factor do you want to --
14 safety factor do you want to add? I don't think
15 there's a right answer to it. I think the issue is the
16 safety issue.

17 And the second is, the Academy did not comment about a
18 hepatitis B surface-antigen-negative mom who is in a
19 high-risk group or the family is in a high-risk group.

20 In other words, someone from Africa, for instance.
21 And the Public Health Service said vaccinate them,

1 vaccinate them at term. We did not comment on it and
2 we specifically didn't comment on it. There's really
3 two things that go into the equation about that.
4 One is that the risk of horizontal transmission during
5 the first two years of life is very, very small. And
6 we are both, both the Public Health System and the
7 American Academy of Pediatrics, strongly recommending
8 that you finish out your immunization, your three-dose
9 hepatitis B immunization by 18 months of age.
10 But the Public Health Service had data
11 that -- at least when we were making the decisions we were
12 not aware of, that said that if you do not start the
13 vaccination at birth, that the completion of the three-
14 dose series goes down from 96 percent to 81 percent.
15 So if you're talking as the American Academy of
16 Pediatrics does to its pediatricians, and you're saying
17 you can make that individual decision based on your
18 family, what's the chance that they're going to come
19 back versus not come back, versus you're dealing with
20 it from a public health perspective and you know that
21 number, you could understand where the difference comes

1 from.

2 I do think there are remaining issues, and I think
3 Roger highlighted a number of them very well, but one
4 that I'll want to get back to is, when you have
5 emergent situations -- And remember, this was not the
6 only emergent situation. Rotavirus was happening at
7 the same time. I'm not kidding you when I tell you I
8 hung by phone booths for hours at a time, sitting on a
9 phone in Canada, going around Canada and hanging by the
10 phone, and we're trying to deal with this on as fast as
11 possible basis as we can as we're getting the
12 information.

13 So how do you go through the approval process when the
14 approval process is very different? The ACIP cannot
15 come together as a committee without publishing it in
16 Federal Registry. We need to deal with that because
17 this may not be the last emergency that we have to deal
18 with.

19 What is the mercury exposure from other sources? We
20 still haven't dealt with that. And, I mean, we put the
21 data in. I might as well say it. A six-ounce can of

1 tuna has 17 micrograms of mercury in it, on average.
2 There's obviously a range to it. What does that mean
3 for a pregnant woman? What does it mean to the fetus?
4 I sit on the ACIP Influenza Working Group, and we
5 discussed the issue, what are we going to do with the
6 pregnant mom? Well, the pregnant mom in the second and
7 third trimester has a substantially higher risk for flu
8 than does a non-pregnant mom. So based on our
9 principles, we would recommend giving the flu vaccine,
10 and that's what the working group is going to advise.
11 Now, that doesn't mean the Public Health Service has to
12 agree to it, but that raises the question of "Is that
13 the right decision?" -- I think so -- but do we need to
14 put other things in the consent form to inform a parent
15 or an expectant mom about that.

16 The education of the public. I will tell you that we
17 received a number of letters from angry pediatricians
18 because they don't use computers and the public -- some
19 of the public does, and the public learned about it
20 before the pediatrician did.

21 And I don't know a way of solving it. We actually put

1 out something that's called the Peds Com, which takes
2 several days to get out and put out, but it is
3 expensive and it's much better and much faster to do it
4 by computer, and it's much cheaper to do it by
5 computer. Those are all issues that come about when
6 you're dealing with an emergent situation.

7 I personally think that the AAP and the Public Health
8 System worked well together during these two emergent
9 situations, and I've actually learned a lot from the
10 process and enjoyed working with them.

11 That's all.

12 **DR. MODLIN:** Thank you, Jon.

13 Our next speaker is Peggy Webster, who is Director of
14 the National Coalition on Adult Immunization, and she
15 will give us the perspective of that group.

16 **DR. WEBSTER:** Thank you, Dr. Modlin.

17 Good morning. I just came to represent the National
18 Coalition for Adult Immunizations this morning and give
19 you a statement of where we stand on these issues of
20 thimerosal in vaccines. What I have here is nothing
21 earth-shattering -- I'll give you that -- but let me

1 just read to you what we put together here, and I
2 appreciate any comments that you might have afterward.
3 While thimerosal has been used as a preservative in
4 many vaccines for many decades without apparent ill
5 effect, it is nonetheless imperative that science and
6 medicine continually seek safer and more effective
7 medicines and procedures. With this in mind, we must
8 make reasoned progress in the area of vaccines and
9 vaccine research. On the one hand, each of us no doubt
10 feels some level of concern in knowing that a small
11 amount of a mercurial compound is present in the
12 vaccines that we give to children, pregnant women,
13 nursing women, and adults. On the other hand, it is
14 also the case that it is difficult to find any
15 definitive data suggesting that the use of such
16 compounds has resulted in any direct harm to humans.
17 We must also recognize that changing from one
18 preservative to another is not without some level of
19 risk itself, no matter how small, and may lead to other
20 potentially unknown side effects.
21 With this understanding, our organization would like to

1 emphasize concerns about the use of thimerosal in two
2 settings.

3 First, the Advisory Committee on Immunization Practices
4 has rightly made the national recommendation that women
5 who will be beyond their first trimester of pregnancy
6 during the influenza season receive the influenza
7 vaccination. Those who have medical conditions that
8 increase their risk for complications from influenza
9 should be vaccinated before the beginning of the
10 influenza season regardless of the stage of pregnancy.

11 It is important to note that all of the licensed
12 influenza vaccines in the U.S. do contain thimerosal.
13 There has been no reason to believe that there may be
14 adverse fetal effects associated with using thimerosal-
15 containing vaccinations. The NCAI agrees with the ACIP
16 that more data are needed in this special circumstance.

17 Second, there is a small population of vaccine
18 recipients who have an allergic sensitivity to
19 thimerosal. Even when allergy testing does indicate
20 hypersensitivity to thimerosal, most patients do not
21 develop reactions when given thimerosal-containing

1 vaccines. If reactions do develop, they almost always
2 manifest as local reactions, but, nonetheless, can
3 discourage both patient and provider from further
4 immunization.

5 In effect, the use of thimerosal-containing vaccines
6 means that a small proportion of the population cannot
7 or will not receive vaccines which protect them against
8 the morbidity and mortality of many otherwise vaccine-
9 preventable diseases.

10 The National Coalition for Adult Immunization is an
11 advocacy group that is committed to decreasing the rate
12 of vaccine-preventable diseases in adolescents and
13 adults, and is therefore in support of the
14 recommendation to continue utilizing vaccines until
15 further guidelines are established.

16 In the meantime, NCAI calls for and supports the
17 following steps:

18 First we support the recommendation from the Public
19 Health Service and FDA that all vaccine manufacturers
20 submit a plan for the elimination of all mercury-
21 containing compounds from human vaccines as soon as

1 possible.

2 Second, we support and call for further research into
3 the benefits and risks of these compounds in
4 individuals and their potential impact on public
5 health, particularly in regards to the possibility of
6 neurodevelopmental effects on the developing fetus.

7 Third, we support and call for the development of
8 communication materials for health care providers and
9 patients that clearly and fairly articulate the current
10 controversy while maintaining public confidence in the
11 enormous individual and societal benefits of
12 immunization.

13 Finally, we support the Public Health Service and the
14 American Association of Pediatrics call for expedited
15 FDA review of manufacturers' supplements to their
16 product license applications which eliminate or reduce
17 the mercury content of their vaccines.

18 Thank you for the opportunity to participate.

19 **DR. MODLIN:** Thank you, Dr. Webster.

20 Our next speaker will be Dr. Neal Halsey. Neal is
21 representing the Institute for Vaccine Safety at Johns

1 Hopkins University School of Public Health and Hygiene.

2 **DR. HALSEY:** Thank you very much, John.

3 I didn't come prepared with a rebuttal for Jon
4 Abramson. I should have thought more about it, but I
5 can't come up with jokes quite that quickly, but I
6 agree entirely with what Jon said. I also agree with
7 almost everything that Roger Bernier presented -- I
8 can't find him in the audience right now -- and we can
9 talk about areas where we do disagree, but I do think
10 that the business of providing guidelines to physicians
11 and parents is unfinished during this transition
12 period. I'm asked to comment on what the perspective
13 is of the Institute for Vaccine Safety during the
14 transition period.

15 Well, the position is fairly simple, and that is that
16 all children should be protected against vaccine-
17 preventable diseases using the safest possible
18 vaccines. Actually, I think that everybody in the room
19 would agree with that.

20 The objective in the transition period is to minimize
21 any potential risks that might be there, but, also, as

1 many people have stated, to maintain public confidence
2 in vaccines, the agencies, the federal agencies
3 responsible for both vaccine safety and for delivery of
4 vaccines, but also to the physicians who not only are
5 responsible for providing those vaccines, but also for
6 advice and guidance to parents of children who are
7 going to be receiving these vaccines.

8 We do need to pay attention to what's happened in the
9 public in recent years over the increased concern about
10 product safety in general, and I won't spend the time
11 to go through all of these examples, but we do need to
12 be aware that there's been concern about environmental
13 exposures of a variety of types, food contamination,
14 automobile safety, toys, as well as drugs and vaccines.
15 Where these have been handled well, it increases the
16 confidence of the Public Health Service and government
17 in general, but there are several examples of where
18 they have not been handled as well as they could have
19 been, especially in Europe, with loss of public
20 confidence in our government agencies that are
21 responsible for protection of safety, and we don't want

1 that to happen in this situation or any similar
2 situation.

3 My personal belief is that we should follow the
4 examples of what some of the producers of food,
5 particularly children's food, baby food, in this case,
6 from the representative of Gerber Foods, the CEO of
7 Novartis, the parent company, in removing some
8 chemicals, which, personally, I don't think carry any
9 risk for those children. But their philosophy is that
10 "We want a mother to buy our product and have no
11 concern about this issue." We should adopt similar
12 philosophies with regard to vaccines.

13 I'm going to make seven points, and I will come back to
14 each of these in detail and only mention them at the
15 beginning.

16 First, that I think the mercury content of vaccines
17 should be in the package label.

18 Second, that all children are not created equal with
19 regard to their risk of exposure to mercury.

20 Third, that I think hepatitis B has been unfairly
21 targeted and assumed to be in some situations the only

1 problem that occurs with regard to thimerosal.

2 I think we need to do better -- a better job of
3 informing both physicians and parents about the
4 uncertainties that we've talked about and the options
5 that are available to them to help deal with the
6 potential or perceived possible risk. Everyone has
7 said, and we fully agree, that there should be an
8 expedited review of products with -- by the FDA with
9 reduced or no thimerosal, and FDA has committed to
10 that. So they don't really need us to tell them that.

11
12 I think manufacturers should look very hard at
13 providing unit dosing of vaccines whenever possible.

14 I think there is a problem at the FDA that does need to
15 be addressed and that we need additional resources and
16 scientists to address vaccine safety.

17 To go back over some of these issues, now, the first is
18 the product labeling. I had to ask myself why someone
19 who -- I felt I knew a fair amount about vaccines over
20 the past 25 years and knew something about
21 environmental exposures, why I didn't put it together.

1 Why I didn't realize how much mercury was actually in
2 vaccines. And I think it's because the product label
3 indicates a concentration of thimerosal of 1 to 10,000,
4 or a .01 percent.

5 And as Leslie Ball walked us through, you have to go
6 through a two- or three- or four-step calculation, and
7 you have to know the molecular weight of thimerosal to
8 come up with the 25 micrograms for mercury.

9 Since mercury is the biological agent, the biological
10 product that's there, and we have guidelines for the
11 amounts of mercury that people should be exposed to,
12 that should be in the product label.

13 There are many factors that are associated with mercury
14 toxicity, and that's what I mean by not all children
15 are created equal with regard to their susceptibility.

16 Many of these were discussed yesterday, so I won't go
17 back over all of them, but there are differences in
18 terms of the age of exposure, the weight of children,
19 other mercury exposures, differences potentially in
20 metabolism and excretion rates on an individual basis,
21 not for the products. No one has really addressed the

1 very well the genetic predisposition to increased risk
2 of potential toxicity.

3 We can look most clearly at the weights of children,
4 and I've picked girls here. Boys weigh slightly more
5 than girls, but if we're looking at who may be the
6 highest-risk population, the children who are the
7 smallest, are the three standard deviations below the
8 norm, their birth weight of 1.8 kilos, there's a
9 difference, a more than two-fold difference, in the
10 weights of these children, and if exposure to mercury
11 is a weight-based phenomenon when you get a fixed dose,
12 then that two-fold -- that is an important concern.
13 That two-fold difference persists all the way out to
14 almost six months of age. And we need to realize that
15 it's the smallest children that I think that we have to
16 be preparing our guidelines and decisions as to what we
17 do with them.

18 If we take those weights of children and then apply the
19 fixed doses and look at the worst-case scenario of
20 children who may be getting all thimerosal products, or
21 prior to the most recent change in the recommendations,

1 it plots out like this. And since sending Dr. Clarkson
2 and Dr. Raub the data on the actual weights, I did
3 adjust so that these children were getting hepatitis B
4 when they weighed two kilograms.

5 We have, through the recent guidelines, addressed this
6 exposure here, but, in fact, the exposure that's
7 occurring at two months of age is several-fold higher
8 than that exposure that's occurring at birth. And,
9 yes, the infant is slightly older and therefore may be
10 somewhat less, if there is a risk per dose delivered at
11 that time, then this is something that I think we still
12 have to be concerned about and decide whether or not
13 anything further with regard to advice needs to be
14 given.

15 I do differ with what Roger said and what I think the
16 Public Health Service has concluded, that we can take
17 the exposures and cumulate them over a year or over a
18 six-month period of time. The evidence available about
19 mercury toxicity doesn't support that. Yes, that's one
20 aspect, the cumulative exposure, but there is the
21 problem of an individual exposure at an individual time

1 from the acute toxicity data that exists.

2 An exposure with a fixed dose, 62.5 micrograms at two
3 months of age, is different than an exposure at six
4 months of age, or if that was at nine months or twelve
5 months.

6 So I really question the philosophy that it doesn't
7 matter when you got it or if you got a significant
8 portion of that, one-third of it all in one day, that
9 you really can take and look at that exposure over a
10 six-month or a twelve-month period. So that's where I
11 do differ.

12 I do not know that any of the guidelines that have been
13 written by any of the agencies say that it's okay. Can
14 you really get all 200 micrograms in the same day? I
15 don't see that written any place, and I don't hear that
16 from the people who have been responsible for
17 developing those guidelines.

18 Which guidelines should be applied? We've been through
19 this too many times. You've seen this similar slide.
20 The Public Health Service has chosen the ATSDR, which
21 is a little more liberal with regard to the allowable

1 exposures in the EPA. The WHO is quite similar to the
2 EPA, as we have seen, with regard to those exposures.
3 But over how much time can you take a single exposure
4 and then say it's okay to get this over a day, a week,
5 a month, or a year? We don't know. That's an unknown.
6 The choice of the ATSDR guideline, which is based upon
7 the Seychelle data, made sense at the time that it was
8 done. The process was a good process that they used.
9 But does it mean that we should ignore data that have
10 been generated since then, and especially the follow-up
11 in the Faroes Islands? And does it mean that it isn't
12 going to change? The Faroe Island data were generated
13 when these children were 5.5 years, and they were
14 generated looking mostly at global I.Q. And as we
15 heard from Dr. Lucier, there will be additional follow-
16 up and there will be harmonization of the methods to
17 evaluate these children. So they'll do some of the
18 more domain-specific analyses that were done in the
19 Faroe Islands that revealed those very subtle defects
20 that were picked up. So it's an older age in the Faroe
21 Islands and a more specific analyses that were done.

1 And equally, or, in fact, far more important, as Dr.
2 Lucier mentioned and as Dr. Clarkson mentioned, there
3 is the intermittent exposure that took place in the
4 Faroe Island where it was coming a lot at one time or
5 at monthly doses. And is that the explanation for
6 finding problems in children at seven years of age that
7 were not detected in the Seychelles at 5.5 years?
8 Nobody knows that, but it certainly is one of the
9 hypotheses that might explain the differences in the
10 exposures and we must take it into account.

11 So I don't think that the Public Health Service means
12 we should ignore all of these data, but we do need to
13 be aware that they're there and take them into account
14 and realize that more data will be forthcoming. And
15 what will happen in two years' time if all of the
16 experts review it and say, you know, we really should
17 be using the Faroe Island data as the exposure, how
18 will we be perceived?

19 And again, these defects that are being detected are
20 very subtle defects, and they're not going to be
21 detected without these very sophisticated testings that

1 was done.

2 Some interesting observations is that the males are
3 more susceptible than females. I think that's a whole
4 area of research that these groups will potentially
5 look at, and finding. This is the finger-tapping test
6 that was done, cumulative amount, both hands, easier to
7 measure differences than one hand. In other words,
8 again, you won't find these with less sophisticated
9 testing.

10 If we accept or use the ATSDR guidelines and we
11 superimpose those on these exposures and we put the
12 daily, the weekly, or the monthly exposure here, we can
13 see that at two months of age we're giving at a single
14 day more than the total monthly allowable exposure for
15 the ATSDR guidelines. And, in fact, the smallest of
16 infants represented in the green bars are receiving
17 almost three times, almost three months' worth of
18 exposure on a single day. Is that really -- I haven't
19 heard ATSDR say that that's really okay to do. I'm not
20 convinced that it really is. And if we were to apply
21 the EPA guidelines or the WHO more recent guidelines,

1 they are one-third of this. We're giving eight times
2 the maximum exposure that they would give you for a
3 month. Can you get six or eight months exposure in a
4 single day? I don't think that exposure at two months
5 of age can -- You can't take all of these over six
6 months or a year and average them.

7 We haven't told physicians more precisely what they can
8 do to help reduce that exposure. And if we simply
9 limited it to one thimerosal-containing product that
10 was given at 2, 4, and 6 months of age, it would be
11 DTaP or HIB, then you can reduce this to less than --
12 you can get less than the total monthly exposure for
13 all but the very smallest of infants.

14 If we actually just gave the hepatitis B vaccine and
15 said not use the other two products, then you can get
16 it down below the weekly exposure for almost all
17 infants.

18 And we do have the option that, in many situations,
19 where you don't have to give any thimerosal. And
20 everybody understands that goal, but it actually is an
21 option that's available today. We really haven't told

1 everybody that that's something that you can do.
2 We've talked about all of the uncertainties. There are
3 many. And again, there's not time to go through all of
4 them, but we do need to focus on the other mercury
5 exposures and which this exposure is added on top of.
6 We haven't really touched on any of the data on the
7 potential effect on mild subtle things with regard to
8 the immune system. Those data are going to be
9 forthcoming in the next two years from various groups.
10 With regard to other mercury exposures, this comes
11 directly from the EPA report to Congress, the key point
12 is that the majority of the population is getting
13 relatively low-to-moderate exposures. But in this
14 country we have some populations that have very high
15 levels of fish intake on a regular basis. And as we
16 heard yesterday, FDA estimates that about 7 percent of
17 women of childbearing age are already consuming fish
18 enough that it would give them more than their
19 guidelines, .1 microgram per kilogram per day. So any
20 additional exposure we give them from vaccines is on
21 top of that baseline that they have set with a safety

1 factor included.

2 But they also note in the report that 1 percent are
3 receiving more than .37 micrograms per kilo per day.
4 So there's 1 percent of pregnant women out there who
5 are already getting more than what the ATSDR guideline
6 is. And again, what we give them is added on top of
7 that, and these children are being born with that
8 exposure and some are getting this continued exposure
9 through breast milk.

10 After all of the flurry of activity took place in late
11 June and early July, I did take a vacation, went off to
12 Maine to try to do a little canoeing and a little
13 fishing and having some fun, only to come across these
14 signs that says you can't forget about mercury. And,
15 in fact, for the inland waters in much of the east
16 coast of Maine, you're advised not to eat the fish at
17 all if you're a pregnant woman, a nursing woman, or a
18 child who's less than eight years of age. So there are
19 advisories out there from the health departments
20 indicating "limit your exposure to mercury," but
21 they're not being followed. The general consensus in

1 the local population is that these are largely ignored
2 by many of the local populations.

3 To change to one of the other topics about thimerosal,
4 it's not the perfect preservative. It doesn't totally
5 solve the problem. There are numerous clusters of
6 cases of group A strep disease and presumably other --
7 one, I think, of other bacteria that have occurred. So
8 it doesn't solve the problem.

9 I personally believe that the manufacturers need to
10 move more toward unit dosing in this country whenever
11 possible. And not only is the benefit from
12 preservatives being not needed in most situations, but
13 there are the reduced errors due to reconstitution that
14 we heard a bit about earlier today. And again, we
15 don't need to go through all of those. There will be
16 another session this fall on some of those issues.
17 There are drawbacks, and these are major limitations
18 that -- and that's increased space requirements in the
19 refrigerator, but I don't think they're quite as bad as
20 what John Clements was telling us. There are some
21 technologies that can reduce the amount of space that's

1 going to be required to store unit dosing. There will
2 be increased costs, and I recognize that as a major
3 problem for developing countries, but I think that we
4 do need to help in terms of addressing that issue. We
5 need to look at it from this country.

6 So to maintain public confidence in vaccines and people
7 giving advice about vaccines, I think we should put the
8 mercury content in the label. I think we need to
9 modify the vaccine information statements. That is our
10 primary means of communication with families about any
11 potential or perceived risks. We don't have it in
12 there now. I realize the process is long to put it in,
13 but I think that has to be done as soon as possible.

14 I also think physicians should be given more precise
15 guidelines over maximum allowable exposures at each
16 age. Can we really have recommendations for the
17 highest risk and have physicians looking at fish
18 consumption and other things? The Academy of
19 Pediatrics is developing additional guidelines on
20 reduction of mercury exposure from all sources. Those
21 won't be available for six to nine months. I don't

1 know what the time will be there, but do we need to
2 have separate guidelines for immunization for those
3 children versus others? In general we have said, no,
4 we can't do that. We must make guidelines for
5 everybody that will be applicable to all of the
6 populations.

7 So my personal belief is that we should do what was
8 done in Europe, that we should give a preference for
9 thimerosal-free vaccines for immunization of infants in
10 this country.

11 The last point I'll make is that we need good science
12 to be used in making these decisions, and that good
13 science has to come from all of our federal agencies.
14 As I looked into what was going on at FDA and research
15 into alternative preservatives, research into other
16 ways to approach this and who is going to be reviewing
17 these applications that were all asking for or
18 demanding rapid review, what is the research budget at
19 CBER? The research budget has been cut in the last
20 five years to one-third of what it was before. Instead
21 of being 20 percent more just to keep up with inflation

1 in that period of time, it's been cut to one-third. I
2 don't know why. I don't know who's responsible, but I
3 hope somebody goes to Congress and says that this is
4 wrong.

5 Thank you very much.

6 (APPLAUSE)

7 **DR. MODLIN:** Thanks very much, Neal.

8 The next presentation will actually be by Dr. Bruce
9 Gellen, who is representing the Infectious Disease
10 Society.

11 **DR. GELLEN:** Thank you. I am speaking for the
12 Infectious Disease Society because, as many of you
13 know, about a year ago we began a project in
14 conjunction with the Pediatric Infectious Disease
15 Society and now joined by the American Academy of
16 Pediatrics that's really trying to look at this issue
17 in a broader way of trying to gauge what the current
18 level of confidence is in our vaccines and immunization
19 program, and by that, to try to see what we can do to
20 maintain or build the confidence in those programs.
21 So, with that, the area of communication and education

1 has really been a focal point.

2 Sitting through here for a couple of days, I'm
3 impressed that you can never stop learning the lessons,
4 and I think I'll talk a little bit about those, but one
5 of the important lessons I learned this morning is that
6 if you chair these AAP committees, you can never go on
7 vacation. Poor Jon was strung out at every phone booth
8 that was in Canada and Neal finds signs in the middle
9 of Maine that tells him he needs to go back and do
10 another PowerPoint presentation.

11 And the final lesson I learned is it sounds like CBER
12 needs to invest in Microsoft to try to help some of
13 their budget requirements.

14 But I think that Sam outlined some of the highlights I
15 want to just underscore, and he did that with his last
16 slide, that the handwriting's on the wall. I think
17 that that really tells us that it's our responsibility
18 to see that it's there, to read it, to interpret it,
19 and then to effectively communicate it to all the
20 people who really need that. As has been outlined by
21 several on the previous panel and at various points

1 throughout this session, that's the public health
2 community, the clinicians, the parents, the media, and
3 to legislators.

4 I think that we've had an interesting opportunity to
5 interact with colleagues from the environmental
6 toxicology world because, as I've been learning the
7 lessons of risk communications, they're the people who
8 have been doing this for a lot longer than we have, and
9 now we have recognized that that's a part of the
10 business that we need to get into.

11 As the face of the disease has gone away, there is
12 increasing concern about the risks, both real and
13 potential and imagined, of the vaccines, and that we
14 need to address those in the same way the environmental
15 risks come up all the time, and I'll bet you can't open
16 any newspaper in this country where there's some
17 headline about something that you may be exposed to
18 that's causing some ill health.

19 So I think that we've learned some lessons. We've
20 learned some lessons about the development and approach
21 to guidelines and how that can guide not only policy

1 decisions, but should also guide communication about
2 those decisions.

3 And finally, I think, under the category of lessons
4 learned, from the very beginning of this session
5 yesterday, there were questions about whether or not
6 the decisions that have been made are up for grabs or
7 are reversible, depending on what we heard.

8 I think that we all had the subtle hope that a meeting
9 like this that brings together the world experts would
10 give us the answer to guide us, and I think that if you
11 had heard what I've heard, that we don't have
12 absolutely clear answers and the hopes that a meeting
13 like this would be done in a -- would bring together
14 all those people that would provide that kind of
15 guidance wasn't going to happen because uncertainties
16 remain. And while everybody keeps pointing to Gina to
17 tell us what those uncertainties are, we've heard them
18 and a number of people have highlighted them, but I
19 think that we know that that's what this arena of risk
20 communication is about, which is communicating making
21 good decisions in the absence of complete information.

1 And I think that we also understand that when faced
2 with an issue, not making a decision or ignoring it or
3 delaying it is, in fact, making a decision.

4 And I think finally what we also need to be more
5 transparent and communicative about is the process that
6 we go -- that we undergo when these things come up.

7 Jon highlighted that, and I think that that's really an
8 issue that we really should be discussing: what do you
9 in these emergency situations? And there will be some
10 that will be far more emergent than this, I imagine, in
11 vaccines and other issues, but I do think that that's
12 something that we really need to address, of how you
13 can, when faced with an emergency, deal with that in a
14 responsible fashion and make moves in a way -- make
15 moves and communicate those moves despite uncertain
16 information.

17 So I think that we've learned that there are health
18 risks of mercury-containing compounds. We have the
19 desire, all of us, to reduce those risks from all
20 sources that we can, and that with a limited data, we
21 are going to be forced to make assumptions and

1 extrapolations, and there may be differences in how
2 people handle each of those, but that we then need to
3 continue to do our best to be as transparent about all
4 the -- about the process, and to let people know that
5 there actually is a process in place that's looking at
6 these things. I think we have heard that from a number
7 of speakers as well, that it's not as though there are
8 not systems in place that recognize this. And I think
9 that, as Jon highlighted, the fact that this went on,
10 essentially concurrent with the issue of rotavirus,
11 highlighted that to all of us.

12 We have had a number of these, as we've discussed in
13 the past, quote, "case studies," and I think that we
14 really need to take a hard look at the case studies
15 that we've been presented to see what lessons we can
16 learn for the next time and how we can go about making
17 good decisions based on the best available science and
18 communicate those decisions though there's still
19 uncertainty.

20 Thank you.

21 **DR. MODLIN:** Thank you, Bruce.

1 The final presentation will be from the Association for
2 State and Territorial Health Officials. The
3 presentation will be made by Claire Hannon, who is
4 Director of Immunization Policy for that organization.

5 **MS. HANNON:** Thanks. The Association of State and
6 Territorial Health Officials is the association that
7 represents the state health official or the comparative
8 senior executive in each state health department in the
9 territories, just so you know who we are.

10 John Williamson was scheduled to be here today, but
11 unfortunately he couldn't make it. He's from Alabama,
12 and they had a legislative issue, as we all know.

13 ASTHO doesn't have a specific policy at this time on
14 thimerosal, so I just wanted to give you some
15 background, how we reacted, and a sense of what state
16 health officials feel about the issue.

17 Vaccine policies are decided on a state level, and for
18 that reason, ASTHO still maintains clear support for
19 state flexibility.

20 The ASTHO organization works to make sure that states
21 have the best information available, and we provide an

1 opportunity for health officials to work with partners
2 and each other to build consensus. We did work quickly
3 on the thimerosal issue and gave state health
4 departments to discuss the issues amongst themselves
5 and with CDC.

6 As I said, we don't have existing policy. And amongst
7 all these discussions with the state health officials,
8 we were not able to reach consensus on specific new
9 policies in such a limited amount of time in reaction
10 to thimerosal.

11 So for that reason, states are using the available
12 science, as well as the CDC and AAP recommendations, to
13 formulate their own policy on a state-by-state basis.

14 At this point, my discussions with state health
15 officials I think would indicate that they don't see a
16 serious cause for concern at the current level of
17 thimerosal but believe it is prudent to reduce or
18 eliminate thimerosal, given that new vaccines with
19 varying manufacturing needs can be expected in the
20 future.

21 We are very concerned with maintaining immunization

1 coverage, protecting infants from disease, and
2 maintaining public trust. And again, we, as the
3 organization of ASTHO, support consensus building based
4 on science, information sharing, communication among
5 states and all the other parties involved.

6 Just to add a little bit of state perspective, I spoke
7 with Dr. Natalie Smith, who is here today from the
8 California State Health Department. She's a member of
9 the Association of Immunization Managers, and they've
10 also been holding discussions over the last two weeks
11 or so about thimerosal and vaccine safety issues.

12 It does appear that states are taking a variety of
13 approaches in the transition to thimerosal-free
14 vaccine, approaches which are sometimes very different.

15 I think both of our associations are eager to hear the
16 most up-to-date information, including reports from
17 this conference, and share those with the states. The
18 states benefit from clear direction and lead time to
19 implement policy changes.

20 Thanks.

21 **DR. MODLIN:** Thanks, Ms. Hannon.

1 I'm going to ask Roger to come down and join the panel,
2 if you would. And at this point in time, I would like
3 to open this up for questions, for comments. I think
4 members of the audience are certainly welcome to offer
5 their own comments or to direct questions directly to
6 individual members of the panel, and we'll start back
7 here.

8 Bud Anthony? Again, when you do speak, please
9 introduce yourselves prior to your question or comment.
10 Bud?

11 **DR. ANTHONY:** My name is Bud Anthony. I'm with the
12 Biologics Consulting Group in Alexandria.

13 **DR. MODLIN:** Bud, excuse me. I think you may need to
14 turn on the mic there. There's probably a switch right
15 below -- probably up above -- keep going. There you
16 go. It may be easier just to speak from your seat if
17 you have a seat with a microphone.

18 **DR. ANTHONY:** My name is Bud Anthony. I'm with the
19 Biologics Consulting Group in Alexandria. And although
20 Neal has cautioned that hepatitis B has been singled
21 out, and it's certainly not the only vaccine that we're

1 concerned about, but it's my greatest concern, and
2 those concerns were heightened yesterday by the
3 presentation from Dr. Mast, so I have a couple of
4 questions.

5 One has to do with the recommendations for deferring
6 the hepatitis B vaccine in hepatitis B surface-antigen-
7 negative mothers, and that is this: Isn't this policy
8 of selective immunization of infants based upon
9 maternal antibody screening, one that we abandoned
10 almost a decade ago because it did not work?

11 I know the new policy is different. In a perfect
12 world, I'd have no disagreement with it, but it seems
13 to me we're going back to something that did not work
14 very well.

15 My second question is, perhaps, more of a moot
16 question, but as I understand -- as I understood
17 Roger's presentation of the AAP position, it is that
18 when a thimerosal-free hepatitis B vaccine is available
19 that it will be given at two months. Why not give it
20 then to newborns?

21 Thank you.

1 **DR. MODLIN:** Bud, I'm not certain that this is a policy
2 that we have abandoned. I think it's a policy -- for
3 screening pregnant women. I think it's a policy that
4 we have added to. Maybe I'll let Neal -- and,
5 certainly, Neal has been intimately involved with this
6 in the past. Both let Neal and Roger respond.

7 **DR. HALSEY:** Jon is current chair, but --
8 Well, the Academy policy to give the vaccine at birth
9 was based upon a number of issues, and the Academy
10 policy was published in '92, but the Public Health
11 Service was published in '91, and I don't sense from
12 anybody that I've had any contact with that there's any
13 abandonment of that policy. I believe the Joint
14 Statement still has the language in it, although it was
15 modified, that once the thimerosal-free preparations
16 were available, the preferred age will be at birth.
17 The Academy's policy has been that you can initiate it
18 between birth and two months of age, so there was
19 flexibility within the schedule. That's the
20 terminology that was used. But my belief is it makes
21 sense to go back to birth immunization whenever

1 possible as soon as we have a thimerosal-free, but Jon
2 is really the chair and should respond.

3 **DR. ABRAMSON:** Oh, I agree. Let's make it clear why we
4 picked on hepatitis B. It is the one disease in the
5 hepatitis B surface-antigen-negative mom that the
6 infant is at very low risk for. The infant is at risk
7 for pertussis. The infant is at risk for HIB disease.

8 So that is why we picked on hepatitis B, not for any
9 other reason. And we've stated clearly in numerous
10 places that once we have thimerosal-free vaccines, we
11 will go back to recommendations for giving it at birth.

12 **DR. ANTHONY:** Let me respond quickly. My concern is
13 that babies who we all agree need the vaccine will fall
14 through the cracks, and we heard examples of that
15 yesterday. And the selective policy -- I was not privy
16 to the decision, but it's my strong impression that we
17 got away from selective immunization because it did not
18 work.

19 **DR. ABRAMSON:** I don't see us as selectively
20 immunizing. I see us as immunizing at just a delayed
21 period of time. The recommendation is still to get

1 three doses in by 18 months of age.

2 **DR. MODLIN:** Dr. Daum?

3 **DR. DAUM:** Bob Daum from University of Chicago. I've
4 also been impressed -- I think Bruce made the comment
5 of how much out there there is to learn (inaudible) is
6 that there is a big mercury vacuum in your brain and we
7 don't know much about it and (inaudible) learn a lot in
8 a couple of days. And there's obviously a long way to
9 go in terms of understanding what the effects are on
10 the brain and whether this ethylmercury has any effect
11 at all, much less what the effect of methylmercury is.
12 But I'm wondering how this got so quickly translated
13 into a public and private immunization policy. And I
14 read when the Beatles were doing public performance and
15 they actually gave up performing before they broke up,
16 and the reason they gave up performing is because they
17 were having to perform in larger and larger stadiums.
18 And what they found was they couldn't do anything
19 subtle on stage, because if they tried to, no one would
20 see it and no one would understand it. They were
21 performing in 100,000-seat stadiums.

1 And in a way we are performing in a similar stadium,
2 because we make very fine and sweet vaccine
3 implementation policy here in rooms like this, or much
4 smaller ones, and expect pediatricians and public
5 health people around the country, and we've heard also
6 around the world, to go forward with these utterances
7 and carry it out in a crisp, precise clinical activity.
8

9 Well, that's not what happens. I've learned from my
10 activities in inner city Chicago that there are -- it's
11 like playing the telephone game, that people whisper
12 and people read these recommendations and then come
13 away with vastly different interpretations of them and
14 vastly different concepts of them and, therefore, the
15 translation of this is going to have errors and
16 consequences along the lines of what Dr. Watson talked
17 about here yesterday.

18 In addition to that, John, I don't know if you were
19 here yesterday, but we know from our inner city
20 population in Chicago that if you look at kids that
21 received their first dose of hepatitis B vaccine at

1 more than three months of age, only 10.6 percent of
2 those kids have finished the three-dose series by 19
3 months. We also know that if you delayed -- whatever
4 that first intervention is doing, if you delay it and
5 take a (inaudible) in receipt of 4, 3, 1 by two years
6 of age.

7 The bottom line of these two kinds of things is the
8 translation of a sudden change of policy interaction
9 and with, in my view, a relatively minimal amount of
10 information that demands this kind of emergency is that
11 we're going to throw a lot of vaccine programs into
12 confusion.

13 It certainly sounds as if mercury is an issue that we
14 all ought to think about. It certainly sounds as if we
15 all ought to be thinking about how to get a mercury-
16 free vaccine. I'm the first one to stand up and want
17 safer vaccines -- I think that's a crucial part of our
18 program -- but I just don't understand why it was so
19 urgent to shift this immunization policy so quickly.
20 It creates a confusion that you're hearing only distant
21 echoes in this room, because a very few of us are out

1 on the front line doing vaccine implementation. But,
2 nevertheless, I can tell you, it's beginning to sound
3 like a louder and louder noise among the people that I
4 take phone calls from and interact with every day.
5 So I guess that's my comment, and I'd certainly like to
6 hear anybody's response to that.

7 **DR. MODLIN:** Roger?

8 **DR. BERNIER:** I was thinking you probably expected Neal
9 to answer that question, but I'll probably surprise you
10 by trying to tackle it myself.

11 I think what's happened is that -- I've told this to
12 some people -- we've had a paradigm shift in how we
13 think about this preservative. And when I went to
14 leadership classes, I was told paradigm shifts take
15 years. I think we experienced a paradigm shift in
16 days, or maybe weeks at the most.

17 And it has to do with our consciousness being raised
18 about the potential, potential, effects of mercury.
19 Once we had that realization -- And I think in some way
20 there was a new realization for all of us, and some of
21 us came to it for different reasons in different ways.

1
2 I think Neal likes to talk about how, you know, the
3 concentration and the dilution were not an easy way to
4 realize this, but all of us in some way have had a sort
5 of heightened awareness now, and we can't do business
6 as usual. I mean,
7 that's -- While there's not a lot of evidence about harm,
8 and it's a potential thing, it does become a matter of
9 choice and goal and direction that you want to go into.
10 That's how I would tackle it.
11 **DR. MODLIN:** Yes?
12 **DR. RICHARD:** I'm John Richard from the Agency for
13 Toxic Substances and Disease Registry. For Dr. Halsey,
14 you brought up some very good and very germane points
15 that's consideration --
16 **DR. MODLIN:** Apparently, you don't have your microphone
17 on. I'm sorry. Let's try this again.
18 **DR. RICHARD:** Yeah, for Dr. Halsey. I'm John Richard
19 from the Agency for Toxic Substances and Disease
20 Registry.
21 You raised some very good points, and I was just

1 pointing out that those are things that the government
2 health agencies that are involved in this and involved
3 with the analysis for assessment of health effects of
4 mercury have been concerned about and have considered.

5 And I think this afternoon, in the research needs
6 portion of the program, some of those will be
7 addressed.

8 You also raised some questions or asked questions of
9 ATSDR, and real quickly I'd just like to point out
10 three things.

11 One is that in a series of three injections, three
12 vaccinations, the total dose, as I understand it, is
13 62.5 micrograms per child. While that's to the child
14 in the Seychelles study, we looked at the dose that the
15 mothers received every day on the average throughout
16 pregnancy, and that was 78 micrograms per day. Well,
17 that's to the mother, of course, and on a milligram-
18 per-kilogram basis, that's different. But if you take
19 that 78, then that every week they're receiving almost
20 600 micrograms of mercury, and this goes on throughout
21 pregnancy. Not only that, but the methylmercury is --

1 all mercury, or most mercury is accumulated in the
2 fetus at higher levels in the fetal circulation than it
3 is in the maternal circulation.

4 So these were infants or neo -- excuse me, not neonates
5 -- fetuses being exposed throughout critical times in
6 their development, and we're not saying one point of
7 development is more important than the other, or
8 whether it's the beginning of (inaudible) migration
9 early in the third week, or whether it's further into
10 cerebella or cerebral organization, but throughout all
11 those critical points of fetal development, they were
12 exposed to mercury, methylmercury, through high levels
13 of maternal ingestion relative to the levels that we're
14 talking.

15 For what it's worth, methylmercury is believed to be
16 absorbed close to 100 percent, 95 to 100 percent,
17 through the gastrointestinal tract. So those 78
18 micrograms a day is actually an absorbed dose.

19 Two other quick things, then I'd be happy to hear your
20 response, sir.

21 In the Seychelles, by and large, the tests were of

1 global cognitive function. However, the McCarthy
2 scales tests were conducted, and back in November when
3 the workshop was conducted in Raleigh, one of the
4 panels actually examined the data from the McCarthy
5 subscales and they concluded -- And it's in that report
6 that George Lucier said he had available -- that the
7 data from that on a limited -- not limited, they didn't
8 use the term -- but domain-specific effects indicated
9 no domain-specific change in alteration and function as
10 a result of methylmercury.

11 One thing that I think is a misunderstanding, I think
12 there's the impression that EPA used the Iraqi data and
13 that we used the Seychelles data, and that's, in part,
14 correct. We looked at all the data, but from ASTDR's
15 perspective, we actually used the Faroes -- the results
16 of the Faroes study as the basis as the basis of an
17 additional uncertainty factor. So we did look at that
18 and did consider that in our evaluation.

19 That's all I had to say.

20 **DR. HALSEY:** The one thing you haven't done is answered
21 the key question that the physician and the parent have

1 to face on the day of immunization. That is, how much
2 of that exposure can they get on a single day? You
3 haven't given us the answer to that. I would hope that
4 your agency goes back and tries to address that
5 question. Would you really accept getting three months
6 worth of exposure at one time?

7 **DR. MODLIN:** Stan, is it on this issue?

8 **DR. PLOTKIN:** Well, no.

9 **DR. MODLIN:** Okay. Well, we'll come back, then. Dr.
10 Mahaffey?

11 **DR. MAHAFFEY:** Some comments and a couple of points.
12 First of all, while on average the amount of mercury
13 exposure through food is under the EPA .1 microgram per
14 kilogram per day for adult women, it's certainly not an
15 even distribution and, as Dr. Halsey pointed out, there
16 are groups who are far higher with one percent above
17 the ASTDR level. There are also groups within
18 subpopulations who go a great deal higher, and we have
19 some idea of who these subpopulations are. We know
20 that there are people in this country, probably two or
21 three percent, who eat fish just about every day. So

1 while, on average, yes, it's true, the exposures are
2 lower, they're certainly equal.

3 As far as the safety factors go, our safety factor of
4 ten really is aimed at dealing with person-to-person
5 variability and kinetics and differences in
6 susceptibility to the effects of mercury. We started
7 with a dose of mercury in maternal hair is about 11
8 parts per million, which is really up there in the
9 range that WHO indicates there are questions about with
10 respect to vulnerability of the fetus. So that safety
11 factor of ten is designed to deal with differences in
12 susceptibility and kinetics.

13 Finally, the question -- I understood from the comment
14 that the American Academy of Pediatrics is planning to
15 look more broadly at mercury exposures and I would
16 certainly be interested in a description of what those
17 plans are.

18 **DR. MODLIN:** Jon, did you respond to --

19 **DR. ABRAMSON:** Did I understand the question to be,
20 what else we're looking at making recommendations
21 about? It's really outside of the Committee on

1 Infectious Disease. It's a question of should there be
2 other guidelines as far as fish exposure, other sources
3 of mercury exposure. So I'm really not in a position
4 to comment about it.

5 I would like to address for a second just Bob's
6 comment. For at least many of the people on the
7 Committee on Infectious Disease, the crucial deciding
8 factor for us to make a -- to go forth with a
9 recommendation that differed than saying "Leave
10 everything the same" is, at birth, we were giving many-
11 fold higher than recommended by whoever guidelines you
12 want to use. FDA or EPA or ATSDR, it was more than
13 tenfold. And from everything we could hear, it was
14 unclear that there was that kind of safety factor built
15 into the equation. That's the answer from my
16 standpoint.

17 **DR. MODLIN:** Yes?

18 **DR. ROGAN:** I'm Walter Rogan from the National
19 Institute of Environmental Health Sciences and I'll
20 briefly put my hat on as liaison to the Academy
21 Committee on Environmental Health and say we are

1 writing a new mercury statement. We think, but we
2 haven't been cleared, the intention for the statement
3 is in and we haven't been cleared to write it yet, but
4 we will write a new mercury statement. All that other
5 mercury stuff that isn't infectious diseases is ours,
6 so we will do that. That's the only thing I have to
7 say about that. So we'll do that.

8 Take that hat off, I wrote the sentence about the
9 McCarthy scale stuff. I think it's a little unfair to
10 take that one sentence out of the context. I think
11 that, broadly speaking, if you use the Faroe data as
12 opposed to the Seychelle data, you would come up with a
13 lower number because the Faroe data are positive and
14 the Seychelle data are negative. So we, in that
15 committee -- I was the Chair of the Psychometric
16 Endpoint Committee for that meeting -- were
17 uncomfortable dismissing the Faroe data on the basis of
18 those objections that had been brought about on
19 confounding domain-specific scores and things like
20 that. So I don't want the impression left that we
21 thought that because of some decomposition of the

1 McCarthy scales, the Seychelle data were somehow
2 preferable. We ended up saying these are both good
3 studies and you have to take both into account when you
4 look at them.
5 Finally, back to -- It's hard to keep more than two
6 things in my mind at once. Finally, back to risk
7 management and something Dr. Gellen said, I think the -
8 - I think the choice back in June was not between the
9 Public Health Service and the Academy of Pediatrics
10 saying something and, perhaps, producing a change that
11 didn't benefit everybody, but, rather, between -- and
12 saying nothing which would have resulted in everything
13 going along just fine. I think at least the perceived
14 idea was that to say nothing and to have the
15 information that the FDA, during the process of
16 implementing the Modernization Act, had uncovered or
17 analyzed or calculated that these numbers were higher
18 than we had expected would have gone out. There would
19 have been inquiries of physicians, of state health
20 officers, of vaccine programs, of everybody, and that
21 would have gone into a void from -- with no statement

1 from the Public Health Service or the Academy. So it
2 wasn't a question of this could just sort of go along
3 with nobody saying anything. We won't know what the
4 effect of that kind of uncontrolled and unprepared sort
5 of thing would be because it was circumvented by having
6 something in place, however imperfect and done in
7 whatever haste, but I think that the emergency was not
8 a toxicological emergency. It was the fear that the
9 professional people responsible for answering the
10 questions would be unarmed unless something went out
11 from the Academy of Public Health Services.

12 I'm sorry I took so long.

13 **DR. MODLIN:** Thank you. Stan?

14 **DR. PLOTKIN:** At the risk of seeming to pick on Neal,
15 who is partly paranoid by now -- Well, actually, it's a
16 clarification. Neal suggested that the European
17 attitude is to switch to thimerosal-containing vaccines
18 immediately, and I'd like really a clarification from
19 Dr. Teeling because it's my understanding, as I read
20 the CPMP statements, that the ideal is to switch to
21 thimerosal-containing vaccines as soon as possible in

1 terms of working with manufacturers to eliminate the
2 material from the vaccines. I am not aware, and I'd
3 like Dr. Teeling to clarify, that any national or
4 European authorities have instructed physicians to stop
5 using vaccines containing thimerosal.

6 **DR. HALSEY:** Can I clarify what I said, Stan, and then
7 let Dr. Teeling respond? Okay?

8 What I said is I interpret the wording of that
9 statement is that for infants and children there is a
10 preference -- I didn't say stop -- there is a
11 preference for the use of thimerosal. And I have it
12 written in front of me, but, perhaps, Dr. Teeling could
13 deal with that sentence that I was referring to. I
14 didn't say stop and there isn't any order, it's a
15 preference.

16 **DR. PLOTKIN:** I have to say that I think it's clear
17 that we rule our preferring vaccines without it. The
18 issue is, is it an emergency or not?

19 **DR. MODLIN:** I think we better let Dr. Teeling settle
20 the issue. There is a black button there.

21 **DR. TEELING:** I'm quite happy to let everybody else to

1 answer my question. There's no problem.
2 I mean, I think what you're referring to is the
3 sentence, "For vaccination in infants and toddler, the
4 CPMP concluded that although there is no evidence of
5 harm caused by the level of exposure from vaccines, it
6 would be prudent to promote the general use of vaccines
7 without thimerosal and other mercurial-containing
8 preservatives, particularly for single-dose vaccines."
9 So I think you're both right and I think the statement
10 that you're talking about is that this should be done
11 within the shortest possible time frame, but in order
12 to achieve this, we must work in cooperation with the
13 WHO and the European Pharmacopeia as vaccine
14 manufacturers, FDA, et cetera.
15 So I think the prudence is to move to that. We are not
16 recommending stopping vaccinations in the meantime.
17 Now, it does state here that vaccinations should
18 continue according to national legislation. And in
19 reply to the second part of your question, this
20 statement went out on the 8th of July. And certainly,
21 my visit to the CPMP at the end of July, I had not been

1 informed that any national authorities had made a
2 change. However, we did look at -- And I think this is
3 an issue that has been looked at not particularly in an
4 hurry, but is an ongoing issue at the national level,
5 and there is the instance of one particular country,
6 Austria, which had a tick-borne encephalitis, which is
7 a particular type of disease which is very specific to
8 the Austrian population. They use a vaccine for that.

9 And the addition of the tick-borne encephalitis
10 vaccine added an additional burden of thimerosal to
11 their vaccination programs, and I am aware that they
12 have now withdrawn that vaccine and are using a
13 thimerosal-free vaccine which has recently been
14 authorized.

15 So I think it's an ongoing issue in Europe, much more
16 so than it would appear to be here. I think we've been
17 living with this for the last year and a half or so,
18 with this move, and I think we have had communications.

19 Indeed, we have had some vaccines where the companies
20 have already started to put in variations to reduce or
21 eliminate thimerosal from the vaccines. So it's

1 probably a more ongoing issue. I think this statement
2 is from the 8th of the July and, as to hard facts as a
3 result of that, we haven't had anything else yet.

4 **DR. MODLIN:** There you go, a bit of Irish diplomacy.
5 Roger?

6 **DR. BERNIER:** I would just like to one comment to try
7 to give a sense of deliberations of the Public Health
8 Service and the Academy of Pediatrics.

9 One of the big issues, in a situation where you're
10 trying to take something that you believe is safe to
11 make it safer, you are introducing a change, but for
12 the sake of the credibility of the program, there was a
13 big concern about not creating a perception of good
14 vaccines and bad vaccines. And I think that this issue
15 of preference gets into that category, that as we
16 transition, we're trying to avoid the perception that a
17 label of bad vaccine that would be put on a vaccine
18 that contains thimerosal because it was considered to
19 be a safe product. So there was a lot of discussion
20 about this issue. So I think when we talk about
21 preferences, we have to be careful. We all do prefer,

1 but I don't think it's a preference in the sense that
2 we're willing to call things good vaccines, bad
3 vaccines. Now, that was a very important driver for a
4 lot of the deliberations.

5 **DR. MODLIN:** Yes?

6 **DR. HAUSDORF:** I'm Bill Hausdorf with Wyeth-Lederle. I
7 have a question.

8 Yesterday, I was very impressed by the rapidity of the
9 CDC surveying the hepatitis B screening practices, et
10 cetera, in the wake of this change. That was really
11 very impressive to have data like that. I wondered,
12 given Dr. Daum's comments and also anecdotal things
13 that I've heard about physicians misinterpreting the
14 recommendations to assume that thimerosal-free vaccines
15 are indeed evil and they don't use them, whether
16 there's any attempt or plan by CDC to look at the
17 effect of these recommendations on immunization timing
18 or the rates of immunization outside of hepatitis B?
19 Yesterday, Dr. Schwartz presented, I think, a pretty
20 persuasive case, that if you delay DTP or HIB or
21 whatever, you can clearly have a potential problem. I

1 wonder, is the CDC going to be looking at that?

2 **DR. BERNIER:** One of the recommendations in the Joint
3 Statement -- I believe there were six of them. One of
4 them is to carry out surveillance activities for these
5 changes, and that is something that I think CDC is
6 thinking about. Dr. Mast had told me yesterday about
7 planned investigations to look specifically at
8 hepatitis B issues, but at the moment, there's not a
9 detailed action plan. In fact, we're stretched pretty
10 thin doing a lot of these rotavirus investigations and
11 doing a case-control study related to rotavirus, but it
12 was foreseen in the Joint Statement, that there would
13 be surveillance to monitor the implementation to see if
14 any adjustments needed to be made.

15 **DR. MODLIN:** Back of the room? Yes?

16 **DR. GOODMAN:** Yeah, Jessie Goodman from CBER.
17 Just to follow up on a couple of the comments, I think
18 one of the things that may have occurred, and I guess
19 luckily I was out of the country when all this
20 happened, but if I was here I could speak more from
21 firsthand knowledge, is that there is this spectrum of

1 what our public health emergencies are, true public
2 health emergencies, epidemics of pneumococcal disease
3 or exposures to toxic or infectious substances, and
4 then there are potential public health threats. I
5 think this very clearly is a potential public health
6 threat that warrants very careful consideration and,
7 because of the kind of consequences people have talked
8 about, very careful consideration of the response. But
9 under the microscope of the media and public concern
10 and all that, what has tended to happen is that whether
11 something is a potential public health threat or a
12 public health emergency, they're all being handled as
13 public health emergencies. I think although I'm
14 hearing that the agencies all work together well under
15 the circumstances, I would second Bruce's comments,
16 that I think, one, I'd think through carefully if there
17 are any ones we can improve our responses to these
18 kinds of issues, not necessarily critiquing the
19 response to this issue in its particulars, but not
20 falling into that particular trap of everything being a
21 crisis and everything being an emergency. That's

1 really all I wanted to say.

2 **DR. MODLIN:** Thank you. Further comments? Yes, Stan?

3 **DR. MUSIC:** Stan Music, working with Merck at the
4 moment.

5 (LAUGHTER)

6 **DR. MUSIC:** I want to express some concerns about the
7 epidemic of disease that I think we're beginning to see
8 as a result of the controversy. When I hear John
9 Abramson talk about a 3 kilogram normal infant and say
10 on that day we exceed the guide by tenfold or when I
11 heard Roger Bernier say "I haven't heard anybody say
12 differently," I mean, I understand that the complexity
13 is enormous and I think that that's an underestimate.
14 I also want to make it clear that I am speaking
15 professionally, as an epidemiologist with thirty-plus
16 years now, and though I work for Merck, I'm not
17 speaking for Merck. This has not been cleared.
18 I spent twenty-eight years at CDC, mostly infectious
19 disease, mostly outbreaks, mostly training
20 epidemiologists, but in '96, I became the Chief of
21 Environmental Epidemiology from North Carolina and I

1 learned a lot of NOELs and LOELs and mercury in fish
2 and I was responsible for wording of the signs on the
3 creeks that gave the warnings and was very unhappy with
4 the way we had to interact with the regulators and the
5 sort of emphasis on regulation without the true public
6 health effectiveness of making those warnings heedable
7 (sic). It's all over the east coast. It's not just up
8 in Maine. It's in Maryland, it's in North Carolina,
9 it's all the way down to the Gulf Coast.

10 When a MRL, a minimum risk level, or other guideline is
11 applied here, it's -- I think it's being misapplied and
12 I think it's being misapplied because of the way we
13 label slides and because of the shorthand way we have
14 to speak, but we have no data for ethylmercury. So in
15 addition to what has been said, and I respect the
16 rights and the integrity of everybody that said it, I
17 think it's also legitimate to say that when a MRL,
18 which is for chronic exposure for ingestion or
19 inhalation and for methylmercury, is applied to what we
20 are injecting with vaccines, will we get it all on the
21 same day and we, at the same time, ignore any excretion

1 or we assume that it is all totally instantly
2 bioavailable, I think that's an abuse of the MRL and I
3 think we need to make slides say those things and say
4 it the right way so that everybody understands that the
5 shorthand doesn't confuse them.

6 That's the concern, and I want to state it clearly
7 because I am concerned about the epidemic of disease
8 that this controversy is causing. That is, delayed
9 vaccinations are not good.

10 **DR. MODLIN:** Thank you. Dr. Clarkson?

11 **DR. CLARKSON:** I strongly agree with the previous
12 speaker. I think there has been a misuse of these MRLs
13 and guidelines. They are, as the speaker pointed out,
14 intended for chronic long-term exposures. So the
15 number you get for long-term exposure is a daily
16 exposure that goes on continuously, six months, a year,
17 and so on. You can't take that number and apply it to
18 a single day, as apparently has happened by the
19 statement that in a single day they'll get ten times
20 what the guidelines says. The guideline is intended
21 for day after day after day exposures. Let me give you

1 an example.

2 A comment was made about eating six ounces of tuna fish
3 which contains 17 micrograms of mercury. Now, if you
4 take that once, as a pregnant female weighing 60
5 kilograms, the increase in mercury level in blood or
6 tissues would be so small you couldn't measure it. If
7 you took that six ounces day after day for six months
8 to a year, her blood levels would slowly rise until they
9 reach the level consistent with these guidelines, about
10 20 parts per day.

11 So there seems to be a tremendous misunderstanding as
12 to what these guidelines mean, and with the benefit of
13 hindsight, we should write a talk on the kinetics of
14 mercury so that we have some understanding of what the
15 meaning of a day dosage in terms of tissue levels
16 versus the meaning of a six-month dose. And this is --
17 I mean, in this learned audience, it worries me that
18 there's such a misunderstanding of the guidelines.
19 Lord only knows what the general public views these as.

20 (APPLAUSE)

21 **DR. MODLIN:** Yes?

1 **DR. ENGLER:** Dr. Engler. I just want to speak from a
2 clinician's perspective and from an educator, both for
3 physicians and nursing staff.

4 This event -- And I just want to emphasis the last two
5 speakers; I agree a hundred percent -- has really
6 stressed the front lines, once again, in ways that are
7 hard to imagine until you sit in a clinic with a rapid
8 rate of health care delivery challenges you where there
9 is no adequate recognition of the complexity of
10 immunization health care delivery and you very rapidly
11 have thirty-minute visits that are not being counted or
12 are not paid for in any of our systems, trying to
13 answer questions that this illustrious group can't
14 answer. I think that the whole issue of how we
15 translate what the questions are and the words we use
16 have a huge impact, and I want to take a lesson from
17 the latex allergy issue.

18 We've moved away from saying we need to create latex-
19 free environments because it's unrealistic. We talk
20 about latex-safe environments which acknowledge that
21 there is some latex exposure.

1 So just the language of saying thimerosal-free does
2 convict in the layperson's mind and most providers who
3 already don't think much of the vaccines. Some of the
4 worst people who don't want to be immunized are
5 physicians and nurses as a group.

6 Why aren't we talking about thimerosal-safe and
7 recognizing that there is a balancing of issues in that
8 arena? If we're going to make edict, then what about
9 information fact sheets for providers and for the
10 public that are readily available and palatable and
11 let's call them "Draft version 1," so that the edicts
12 that come down are translatable and usable in a quick
13 user-friendly fashion. I think we should enhance the
14 funding for the CDC section that helps write in a
15 language that people understand.

16 If AAP, ACIP, et al. -- And it is very hard to teach
17 people about all these organizations and what they do.

18 I'd love you to give me a teaching slide set on it
19 that's user-friendly for our use. Why not use those
20 people as you're working these rapid-response edicts to
21 create those interim or early VIS version 1 so that as

1 you're evolving these issues, you take the rest of the
2 world with you? When I've been to the Armed Forces
3 Epidemiologic Board, I've said to them, "Do you all
4 care that almost no one knows you exist or what you do
5 and you're twixes never get to anybody who's doing the
6 work?" And that is not just a problem in the military
7 health care system. That is a problem throughout the
8 health care system. Just speaking for, as I say, the
9 nurses and physicians on the front lines, you know, we
10 want to work with you, but it's awfully hard and also
11 challenging.

12 **DR. MODLIN:** Thanks, Dr. Engler? Further comments?
13 Dr. Klein?

14 **DR. KLEIN:** I think one of the positive aspects that
15 we've learned from this experience is that introducing
16 immunization in the nursery is a very positive feature
17 of vaccine utilization and that that lesson should be
18 carried through with hepatitis returning to the nursery
19 at the earliest possible time, but the opportunity to
20 introduce during that period where there is so much
21 positive educational opportunity, I think, is one of

1 the most important things we've learned in the last
2 couple of days.

3 **DR. MODLIN:** Thanks, Jerry. I think on that very
4 positive note, I'll ask that we wind things up and
5 certainly thank our speakers, our panel, and all the
6 participants for their comments. It, indeed, has been
7 a terrific morning and we look forward to a terrific
8 afternoon.

9 We will start back again at 1:30 on the dot.

10 (LUNCH RECESS FROM 12:25 P.M. TO 1:34 P.M.)

11 **DR. MODLIN:** We are, this afternoon, being asked to
12 look even further beyond the issues that we discussed
13 earlier this morning and to begin to develop -- to
14 identify, define, and develop the important issues for
15 research regarding preservatives in vaccines and,
16 specifically, thimerosal. The person that we've asked
17 to lead the discussion this afternoon is Dr. Regina
18 Rabinovich from the National Institutes of Health.
19 Regina actually will take over and moderate the rest of
20 the session for this afternoon. Regina?

21 **DR. RABINOVICH:** Thank you. Can people hear me? I

1 wish Sam Katz was here so I could thank him for the big
2 buildup, but you know what he was really trying to do
3 was set the stage so that you were trying to both
4 listen to the meeting, as well as begin deriving your
5 own conclusions as to what the next steps were. And
6 you've all come here awake from lunch ready to work
7 because I'm going to attempt to define the landscape as
8 I understand it right now. I am not going to attempt
9 to devise or force consensus because I don't think it's
10 doable. Then I'm going to define some of the questions
11 that remained in my mind as I listened to the
12 presentations of pre-clinical, clinical, and public
13 health and industry perspectives.

14 The panel members will each -- Dr. Clarkson, if you
15 could join us up front, so that as each panel member
16 speaks, they'll be up at the front. The panel members
17 will each -- have been asked to speak for several
18 minutes, no more than five or I will cut it off. I
19 have Bill Egan's watch, good interagency collaboration
20 here, and then the real work starts and all of you have
21 to make sure that we have covered what it is we should

1 be considering in terms of research priorities,
2 important questions, what's doable, and what's
3 answerable.

4 I chose to spell "thimerosal" the way I finally learned
5 to spell it, which is the U.S. way, and let me -- Okay.
6 This is just a little part of the vaccine R and D
7 component that I happened to have a slide ready for,
8 but it's to remind me to remind us that when we talk
9 about individual vaccines and when we worry about the
10 vaccine schedule that each of the vaccines has gone
11 through an intensive process of evaluation from Phase I
12 through Phase IV where safety is a consideration as the
13 number of subjects goes up and the questions that
14 you're answering, be it immunogenicity, efficacy, or
15 effectiveness, alter. There's, in reality, a huge
16 oversight process to this part of it, and I think it's
17 true for preclinical and what manufacturers need to do
18 with potency and establishment licensure applications,
19 which you guys don't have to follow anymore, that kind
20 of thing. But it includes people overlooking the
21 trials, people looking at ethics, the safety monitoring

1 boards, and as you go into Phase IV, which is kind of
2 where we are now with the immunization schedule, the
3 post-licensure period -- This is fifty years or sixty
4 years post-licensure -- including the company, the
5 federal agencies, the parents, interests groups, and we
6 all have some interest or another, as well as those
7 people from the National Vaccine Injury Compensation
8 Program.

9 I have to state some principles which I hope, but don't
10 presume, that everyone will agree with. Although some
11 of them are truisms, I think that it's really important
12 to keep those in the context of: What is the next step
13 and what is it important to do?

14 First of all, vaccines are not perfect. Everyone
15 agrees with that, I would hope. Yet, we understand the
16 enormous value of the role of vaccines in preventing
17 disease. That was beautifully stated yesterday.

18 I think what people don't realize unless they've been
19 involved in some process development or evaluation of
20 that process is that GMP, those standards defined by
21 the field of good manufacturing process, are not

1 perfect. Actually, I've seen some studies where you
2 can quantify the rate at which you will have
3 contamination of a vial given different GMP practices,
4 but that it's not zero. It's a quantifiable risk. At
5 the same time, there are both regulatory and field
6 requirements for a preservative in multi-dose vials.
7 There are some questions that we'll come up and things
8 that I still haven't learned after two days of
9 discussion regarding use of multi-dose vials in the
10 public sector, both domestically and globally.
11 I have learned that the ideal preservative does not
12 exist. I was trying to elucidate the characteristics
13 of an ideal preservative. I've got that list for
14 vaccines and antimicrobials, and I decided I really
15 didn't know enough to do that, but, perhaps, it would
16 be helpful to have someone help us by doing that. But
17 the ideal preservative probably does not exist.
18 I think another principle that you should all
19 acknowledge as we are attempting to come up with the
20 required research agenda is that the data that you have
21 heard and the data that we're having to deal with and

1 listen to from the environmental community and the
2 infectious disease community are qualitatively
3 different. As you heard in the afternoon yesterday,
4 you're talking vaccine efficacy. You've got relatively
5 clear endpoints. You've got measurable health effects.

6 And when you're talking to the environmental
7 epidemiologists and environmental health people,
8 they're talking a language which makes sense to them
9 and for us, it's like parts per million and it's
10 modeling with uncertainty factors. Yet, to them, and
11 in the field of environmental epidemiology, many of
12 those approaches, although not driven to consensus,
13 have a validity and a validity that we, in the
14 infectious disease community in evaluating the
15 randomized clinical trials, the gold standard, have
16 difficulty attributing them. It's probably just better
17 to acknowledge that you've got two communities talking
18 across each other.

19 Now, there are some principles that I think I've
20 learned from thimerosal, and if I haven't, please feel
21 free to speak up because this is what I learned and it

1 should be correct. The first is that we have to look
2 at thimerosal in context, and the context is that
3 children do not grow up in a mercury-free bubble. They
4 don't grow up in a mercury-free bubble prenatally and
5 they certainly don't do it postnatally. This is
6 probably my third day-long or -- Well, I don't know if
7 you can group all the conference calls we had in that
8 two-week period into a two-day period, listening to a
9 number of different people talk about thimerosal and
10 realizing that the efforts to decrease mercury exposure
11 in childhood is not something new, that twenty years
12 ago -- I don't remember the date exactly -- there were
13 diaper powders that had mercury in it, in which it
14 wasn't until people recognized that those were deleted
15 from there. So this is not a -- This is not new. We
16 haven't dealt with it in vaccines.

17 I think the principle is that the health goal is to
18 decrease exposure to mercury overall before you get
19 into the issue ethyl versus methyl or inorganic, et
20 cetera.

21 The other principle is that -- Someone asked me on the

1 way in, they said, "Is this thing about coffee not in
2 the room, is that a regulation or a guideline?" I
3 went, "It's a regulation. They'll throw you out of
4 here." That's a regulation. This is not. This is a
5 guideline. I think that I want -- Where's Roger? I
6 want that slide that shows the gray zone, the white
7 zone, because we got it from whoever presented that at
8 the influenza meeting, and I think that's the best
9 graphic to really present. It doesn't matter, .1
10 versus .3, until you start talking in smallest children
11 and then I'm not sure how it matters, but the .1 versus
12 .3 versus .4 are built into how the non-methyl people
13 think about guidelines and what kind of question
14 they're trying to answer when they create guidelines.
15 The environmental community, having listened to three
16 different sets of them -- Or maybe at least three
17 different sets of them -- are not unified in their
18 assessment of ethylmercury. They may be a lot more in
19 consensus about methylmercury, but they've done that on
20 the basis of detailed review, and I don't think we have
21 the data to look at that. This is the scientific

1 issues relevant to have effects from exposure to
2 methylmercury.

3 Two-day meeting full of preclinical primate/human
4 epidemiologic -- we haven't done that for ethylmercury
5 and we won't have the data to do it at this point. I
6 think the last thimerosal principle that the vaccine
7 community -- we're faced to deal with is different from
8 what the environmental folks have to deal with. It's
9 what I call the Caesar's wife principle. And some of
10 those things my dad taught me, but you sort of
11 remember, is that not only did Caesar's wife have to be
12 pure, she had to appear pure. This issue of appearance
13 being everything, that we have to not only be doing
14 what we think we're doing, but to appear and to be able
15 to inform and to be open and transparent about it. I
16 think it's something we need to keep in mind as we go
17 on and define the research.

18 So gaps? Now, gaps are in the context of what I
19 thought were the general principles, and they're not
20 necessarily in the most logical sequence. I sort of
21 started pasting together my thoughts over the past day

1 and a half and the past two hours. Let me just go
2 through them and I promise to distribute them to anyone
3 who wants something a little bit more logical here.
4 None of the mostly methyl exposure epidemiologic
5 studies took into effect -- into measurement of effect,
6 although they have clinical hair samples, et cetera, an
7 understanding of the potential role of immunization of
8 the child of an additional bolus during the time of
9 infancy. This all relates to mercury, in general, and
10 not just necessarily just thimerosal. I'll try to
11 speak with some more relevance specifically to
12 thimerosal on the next slide.

13 The whole issue of the sensitivity of the human in the
14 postnatal period versus the prenatal period, I think
15 there are still a lot of questions unanswered about
16 that. What was clear in the group that evaluated the
17 effects of methylmercury is you have to look not only
18 at the route of exposure and the method of exposure,
19 but with particular relevance to where in the
20 neurocognitive development you think the sensitivity to
21 exposure exists.

1 There were questions made and I think the pediatric
2 community has learned a lot about lead. We're used to
3 thinking about that substance and how to decrease
4 exposure and how to deal with the parts-per-million
5 issue there. That's something I think we know probably
6 more about. Apparently, from a statement made
7 yesterday, the effect of lead is a continuous variable
8 over time. Is that a relevant sort of framework for
9 thinking about mercury? The issue which we have to
10 acknowledge I think remains unanswered: Is toxicity
11 related to peak or chronic exposure? Because the
12 guidelines are based on chronic oral and the exposure
13 that we're talking about is different. It leads to
14 bolus and peak and intermittent.

15 Now, we spent several conference calls arguing about
16 ethyl/methyl and, you know, I was going, "Is there a
17 difference of carbon group? Is that organic
18 concentrate ethyl/methyl?" A colleague of mine, Dr.
19 DeBosky, said, "Yes, but think about it. It makes a
20 really big difference. You're talking ethyl alcohol
21 versus methyl alcohol." Okay. I will admit that I

1 don't know. While it may be perfectly reasonable, in
2 an effort to assure that we're doing is the safest
3 possible, to take the data that we have for
4 methylmercury and to extend the conclusions and the
5 considerations to ethylmercury. I don't know. It's --
6 In thinking of methylmercury in the kinds of settings
7 that are referenced here, the primate data printed on
8 methylmercury exposure which has been associated with
9 motor and sensory changes, alterations in primates, and
10 much less with cognitive effects, led to their
11 conclusion that they needed data on specific domains.
12 Not being
13 a -- What's it called? -- not environmental, but a
14 development specialist, I'm not quite sure what
15 specific domains are. I just know it means more than
16 global assessment of cognitive or any single parameter
17 of development.
18 We need to evaluate potential health impact of prenatal
19 exposure and, if we're going to do that and figure out
20 ways to answer those kinds of questions, it has to be
21 in the context of timing of exposure as it's related to

1 those critical windows of susceptibility during
2 development. That was recommended by the methyl group
3 and I think the ethyl group, and ethyl considerations
4 need to include that.

5 Now, when I start talking about ethylmercury and
6 especially ethylmercury presented intramuscularly, the
7 question really is, how different is it from
8 methylmercury? The potential differences, and I've
9 heard everything from "mercury is mercury" to "it may
10 be 20 percent less toxic" or "really, you need to use
11 it as the model" to "we don't know." And the
12 differences could relate to the potential health
13 effects and the pharmacokinetics, the biological
14 activity, the clinical endpoints one must worry about,
15 the effect of a route of administration, and the dose
16 schedule. And even something as relatively simple to
17 answer -- And we hope to have data not too long from
18 now, Dr. Clarkson -- is, is it excreted and how in
19 infancy? We can't answer that today and we should be
20 able to do that if we're doing our jobs very shortly
21 from now.

1 What levels are reached intramuscular -- after
2 intramuscular doses of childhood vaccines? We can't
3 answer that today. And Dr. Clarkson presented what I'm
4 now calling the Clarkson model, and I think it's
5 something that can be tested and it can be tested with
6 some observational data and we hope to hear more about
7 that.

8 The potential health effects have been learned from
9 either high dose or poisonings. And the one that's
10 acknowledged is the sensitization which is an effect
11 regardless of how ethylmercury is presented, but at low
12 doses, how one can correlate what's known at toxic
13 doses to low doses, to me, is unclear and remains a
14 question.

15 The issue of cumulative levels, it's clear that -- I
16 was worried that after listening to all this, I still
17 don't know what's new to vaccines versus background
18 exposure and what is the most appropriate useful,
19 accurate, truthful time frame for evaluating childhood
20 exposure. You know, in statistics, you can take a dose
21 level and divide it to an average daily dose over six

1 months or over seven months and -- Let's figure out
2 before we start doing the math what the appropriate
3 window is that we're worried about and do it in
4 consultation with the environmental folks who -- and
5 then compare the different strategies to decrease
6 mercury exposure, regardless of source, to that
7 measure.

8 I guess I did ask some questions yesterday trying to
9 understand the impact of some things that we thought we
10 knew, and when statements were made about as to how
11 ethylmercury and methylmercury came apart a little
12 differently, I asked, is this good or bad? Well, it
13 could be good and it could be bad. So the theoretical
14 concerns of nephrotoxicity and neurotoxicity, the brief
15 review of the literature we did showed nephrotoxicity
16 could be more of a concern, but I haven't heard anyone
17 talking about the potential of nephrotoxicity. So
18 these are both theoretical and I think we need more
19 information.

20 At the same time, there are gaps in our knowledge of
21 vaccines and the vaccine field, and that has to do with

1 alternative preservatives. I'm glad to hear that some
2 of the manufacturers have a lot more information than
3 we appear to have on specific pharmacokinetics of
4 methylmercury for -- What is it? -- 2-phenoxy,
5 whatever. I'm not sure it's published. If it isn't,
6 it should be published and we should evaluate it
7 because we have a sixty-year track record with these
8 vaccines. And before we go around running to replace
9 them with another preservative, I think we have lots of
10 questions to be answered. Do that very carefully. It
11 doesn't mean that the data can't be collected or at
12 least wait to hear from our colleagues in the industry
13 that the feasible goal and that this data, the safety
14 data that we're interested in, can be collected.
15 Although we heard a lot about the cost of eliminating
16 and the lack of feasibility of eliminating multi-dose
17 vials, I didn't hear any data and I think it would be
18 useful to know -- Maybe we heard a little bit from WHO,
19 but for the U.S. -- what is the real cost of
20 eliminating the multi-dose vials and going to single-
21 dose vials and what's the real cost in terms of space

1 that's needed to maintain the cold chains for these
2 vaccines? I think you need that for decision-making
3 for the U.S. and I think there's other factors
4 globally. In a country where we
5 are -- I have to quote Dr. Orenstein -- paying three million
6 dollars per dose -- per case of wild-type poliomyelitis
7 to provide -- to avert poliomyelitis due to vaccine, we
8 obviously value vaccine safety and we have the
9 resources to support that kind of approach. So if it's
10 an issue of eliminating multi-dose vials, what are the
11 costs?

12 Can there be novel approaches to limiting mercury
13 content? By this, I meant -- The "novel" word is one
14 that we use at NIH when we want to sort of reach in and
15 have people come up with things that we haven't thought
16 of. By "novel," I mean some suggestions made around
17 how to play with formulation and a way to limit
18 thimerosal, but different kinds of delivery vehicles,
19 total delivery vehicles, which may not need it. Dry
20 powders, DNA vaccines, whatever, novel formulations and
21 approaches to limiting mercury content. Notice that

1 say "limiting" without presumption of value to that of
2 absolute elimination.

3 I think it is possible to get a little bit more data on
4 when in the first two years of life are infants exposed
5 to hepatitis B, because we keep having to come back and
6 discuss that when it comes to the hepatitis B issues.

7 There will be -- There will be -- This is not a
8 question. There will be an ongoing need to conduct an
9 assessment of the cumulative effect of the immunization
10 schedule. And Bruce talked about lessons learned, and
11 I think a lesson learned is as we add and recommend
12 vaccines that we need to look not only at individual
13 vaccines but at the schedule that we're recommending
14 from every perspective. I'm sure we'll continue to be
15 surprised, but we won't be caught with this one again.

16 Data, people have raised "Who's going to do this?" and
17 "Are you going to talk about it?" So let me ask: Do
18 we have data -- I don't think we do -- on which to
19 comment upon the long-term effects on vaccine-level
20 exposure to ethylmercury? I think the first place to
21 look, and I'd ask those communities that have -- the

1 scientific communities that have these databases, can
2 some sort of assessment be made from analysis or
3 evaluation of existing data sources? In other fields
4 like the diabetes issue, we were able to provide, I
5 think, useful analysis from an existing database
6 resulting from a randomized clinical trial in a country
7 in which there was a very detailed and validated
8 diabetes registry to answer a specific question. Are
9 there places we could be looking for information
10 pertaining to this or do we need to go look for novel
11 sources and at what point do we need to go? Do we have
12 enough knowledge about what's going on from animal
13 models or fairly simply measurement of levels in
14 children to have a high enough level of concern that we
15 need to worry about bad health effects as opposed to
16 recognizing the levels that are being administered
17 potentially through vaccines? And I think Roger
18 presented the diversity of the vaccine schedules to say
19 we need to limit exposure.
20 There are different presumptions that lead you to
21 different conclusions.

1 Finally, how to communicate controversial and
2 inconclusive data and at the same time maintain
3 confidence in vaccines. I think we began to hear today
4 what becomes sort of second-guessing what was a very
5 difficult time of a vaccine group trying to understand
6 data that, as you heard over the past two days, was not
7 conclusive, but what was quite worrisome, and to decide
8 when it's compelling enough for some action and at what
9 point and what timing information is distributed.

10 There are lessons learned about systems we need to put
11 in place and how to access our advisory committees
12 rapidly and how to maintain -- Where's Dr. Plotkin?
13 What's the word? -- sang-froid.

14 The charge to the panel -- And I'll ask each speaker to
15 talk for three to five minutes and I have my FDA watch
16 on -- is, number one:

17 What are priorities for research from your perspective?

18 Number two, even if you don't include that in whatever
19 you had thought you were going to present up to now,
20 can you comment on the feasibility and the urgency to
21 do so?

1 I ask you to do this in the constant context of a
2 comment that George Kirwan would make if he was here
3 and he would say, "You know, the most expensive words
4 in the English language are, I wonder if." So you have
5 to put some value on if the "if" that you're trying to
6 answer is, indeed, important for science, for public
7 health, or public policy.

8 The first speaker will be Dr. Clarkson. I think you
9 just need lights on. Do you need to turn this off?

10 **DR. CLARKSON:** With regard to human studies, some
11 suggestions that the group might want to consider,
12 first of all, is this calculation that I did which I
13 think it -- the calculations like this have to be done
14 to assess risk from ethyl and methylmercury. You have
15 to base them on blood levels because all of these
16 guidelines from these various government agencies and
17 so forth all start with toxic blood levels and minimum
18 toxic blood levels and so forth, and they work from
19 them. So what I've given here, for example, is the
20 blood levels that might develop in an infant given
21 these schedules of vaccines. For example, the first

1 shot only raises the blood level to about four parts
2 per billion which is actually about the equivalent of
3 the EPA guideline.

4 So I heard this morning a single dose will be ten times
5 or something the EPA guideline. It's certainly not.

6 It might approach about the EPA guidelines, but as you
7 can see, as it builds up with subsequent doses from the
8 vaccines, it does certainly exceed the EPA guideline by
9 a factor of four or five.

10 But all this is based on all kinds of assumptions. One
11 is that methyl is the same ethyl, which it probably
12 isn't. It's based on the assumption that there's no
13 excretion, and as the Chairperson pointed out, that's
14 something that we should definitely check and I
15 promised to do that, be a good boy.

16 We also should validate hair as a marker for exposure
17 to ethylmercury. That would allow us to do some more
18 population studies to see what hair levels are like in
19 infants, but we have to validate it first. I think
20 that can be done with the infants already available.
21 Hair monitors methylmercury and not inorganic. The

1 hair then could be very useful. It might just monitor
2 the intact ethylmercury in the infant which is probably
3 responsible for the neurological effects, and we'd have
4 to have some other measure for inorganic mercury like a
5 blood sample.

6 As I say, I learned an important thing -- many things
7 from this meeting, but one was that we didn't take into
8 account vaccines in the Seychelles study. I think it's
9 possible now -- Thank you, Dr. Myers -- that it's
10 possible that we may now be able to go back and look at
11 that. We have an enormous amount of behavioral data,
12 clinical data, development data on these kids who are
13 now nine years of age. So we have a huge database. So
14 we might be able to now take a look and see who got
15 vaccines and how much and whether this has an impact on
16 our data, and we might therefore get some -- I hope
17 some useful human data out of this. Of course, this
18 will be a vaccine on top of a substantial dose of
19 methylmercury. So this could be useful, too. When we
20 heard about all other kinds of mercury exposures that
21 kids are exposed to, here you've got a population that