

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 done.

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

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

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

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

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

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

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

8 (LAUGHTER)

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

14 (LAUGHTER)

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

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

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

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

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

1 The question is generated by a comment from Dr.  
2 Mahaffey, but it probably could be commented upon by  
3 many other members of the panel.

4 In discussions leading towards this meeting, it was my  
5 understanding, and I seek clarification, that in  
6 evaluating the neurological deficits that these indeed  
7 were not overt, clinically overt, that it actually took  
8 the detailed neurocognitive evaluation to define them.

9 And you talked about clinically overt neurological  
10 deficits that maternal hair was greater than 20 parts  
11 per million.

12 We've been talking -- using that term as though it  
13 meant something. I realize I no longer know what it  
14 means. So what are we talking about, really, in terms  
15 of neurological deficits?

16 **DR. MAHAFFEY:** Well, I can tell you what we did with  
17 respect to the reference dose, and probably Dr.  
18 Clarkson can comment some, because the reference dose  
19 was based on findings from the Iraqi study. And in  
20 that, that was a poisoning episode of about six months  
21 duration. And while it's been called an acute  
22 exposure, it was certainly one that was long enough to

1 produce fetal effects.

2 Approximately two years later, two of their  
3 neurologists were in Iraq and evaluated as many of the  
4 children they could find who were born from mothers who  
5 were exposed during that epidemic, and, ultimately, I  
6 believe there were 81 maternal-child pairs who were  
7 assessed.

8 The reported paper from Marsh, et al., in 1987 talks  
9 about endpoints such as delays in walking, increased  
10 neurological scores on a standardized neurological  
11 assessment, seizures, delays in talking, and there may  
12 have been another endpoint or two in there.

13 Where the data turned difficult is that the culture in  
14 Iraq and the nomadic living conditions in these  
15 villages made it hard to find these people, as well as  
16 hard to get certain types of information from them. So  
17 there is a level of uncertainty in this data, which we  
18 readily acknowledge, but in terms of clinically  
19 significant endpoints, that's what we're speaking of.

20 **DR. RAUB:** Dr. Clarkson?

21 **DR. CLARKSON:** One of the advantages of prenatal  
22 studies versus studies in adults is you have a much

1 better recapitulation of the dose. You have to make it  
2 over a nine-month period, and so the studies that have  
3 gone on prenatally, like the Faroe studies and the  
4 Seychelles and Iraq, really are a fairly good measure  
5 of what exposure was.

6 The problem with adult studies is that you don't. The  
7 people in the fish-eating populations who are adults  
8 have been exposed all their lives, and you only have a  
9 measure going back a year or two. So it makes  
10 interpretation of a lot of the adults quite difficult.

11 So that there is a tendency, quite understandably,  
12 number one, for risk assessment to be based on prenatal  
13 exposures because of the better measure of dose, a more  
14 clear cut situation, and because the evidence seems to  
15 be the prenatal -- the developing prenatal brain is  
16 more sensitive to methylmercury. It's a big question  
17 that affects this whole debate, which is, how sensitive  
18 the situation is after birth.

19 **DR. MAHAFFEY:** If I could follow up slightly, the  
20 indications that the fetus is more sensitive than the  
21 adult, in part, comes from the Japanese epidemics, in  
22 which mothers, who themselves had very limited evidence

1 of neurological problems, gave birth to infants that  
2 had damage, clinically overt damage.

3 **DR. CLARKSON:** Yeah. The other evidence is also that  
4 in Iraq, when we examined adults -- Now, the advantage  
5 of Iraq, with all its disadvantages, is it was a sort  
6 of a short-term, six-month, or whatever, exposure, to  
7 three months to six months. So we did know, even in  
8 adults in Iraq, what the exposure was, you see, and  
9 what the maximum exposure was, which you don't know in  
10 a fish-eating population. It goes all of their lives.

11  
12 So even with adults in Iraq, you could get their  
13 maximum levels with some, you know, calculations and  
14 some assumptions, but you could come up with something  
15 that at least approximated their actual exposure, and  
16 knowing that this was a one-shot incident, there  
17 probably wasn't much exposure earlier in life.  
18 Now, in that case we got, you might call, I'm an old-  
19 fashioned toxicologist -- a threshold value, say, of  
20 about 100 parts per million in hair with the adults.  
21 Whereas, with the kids, our lowest estimate was as low  
22 as 7 parts per million. Now, there's an error on that,

1 but it's the lower end of our estimate. So from a  
2 quantitative point of view, Iraq also supported the  
3 fact that the prenatal life was more --  
4 Now, the Iraqi thing, too, raised some very interesting  
5 questions about post-natal exposure. We -- Dr.  
6 Amanzaki (phonetic), who was head of pediatrics in  
7 Baghdad, examined a number of children, along with  
8 their staff, who had been exposed post-natally to  
9 mercury in milk. Of course, all feeding of infants  
10 there is from human milk until they can take solid  
11 stuff, which, of course, would be bread.  
12 And these infants, some of them were totally breast-  
13 fed, some which had -- a little older and had some of  
14 the contaminated bread. Some of these infants  
15 developed -- five of them developed blood levels of  
16 1000 parts per billion. And at least from the  
17 pediatrician's point of view, there's nothing wrong  
18 with it. Well, we weren't measuring a five-point drop  
19 in an intelligence score. But from a point of view of  
20 a pediatrician, a pretty competent, experienced  
21 pediatrician, these kids looked normal.  
22 And there was one child -- I think there was a group of

1 15 altogether. I'll have to look up the paper, but it  
2 was about 15 altogether we did. All of them were above  
3 200 in their blood levels and one of them was 1500. It  
4 was heroic. And this raises, first of all, a question  
5 about the actual sensitivity of the post-natal period.

6 I'm not sure I totally agree with my colleague, Dr.  
7 Mahaffey, that you can extrapolate from lead to  
8 mercury. She has been a lead worker after all. I  
9 think the two metals are very different in their  
10 biochemistry and in their mechanism of action, but it  
11 does raise a question about the sensitivity of this  
12 post-natal period.

13 Both the Seychelles and the Faroes, which disagree in  
14 terms of results of prenatal exposures, have not found  
15 any dramatic effects due to post-natal exposures,  
16 either in the Faroes or in the Seychelles, which also  
17 tends to give credence to the idea that the post-natal  
18 period ain't all the sensitive.

19 In fact, one of the most interesting to me of the Faroe  
20 publication, which hasn't been mentioned so far, is  
21 that they looked at children at 12 months of age and  
22 found that the higher the mercury levels in the hair of

1 these kiddies at 12 months, the better off they were.  
2 They achieved their developmental milestones more  
3 rapidly if their mercury was higher. That is kind of  
4 an interesting result.

5 The authors attributed this to a confounder. The  
6 confounder was breast-feeding, because the  
7 more -- the longer the breast-feeding period, the more  
8 mercury they got from the milk and, therefore, the  
9 higher their mercury levels were. They showed that in  
10 the study, that the length of breast-feeding actually  
11 resulted in higher mercury levels. And their  
12 conclusion was, you know, breast feeding is good for  
13 you, it's beneficial, and that was the confounder in  
14 this study. It may have a lot to do with Iraq, too,  
15 that human milk is good for you. And it raises the  
16 other issue that when we look at these numbers, whether  
17 coming from Iraq, from the Seychelles -- The media in  
18 which methylmercury is presented is very important. It  
19 might make a difference to the toxicological outcome.  
20 Certainly, the Faroes group suggested that it was the  
21 sort of protective and beneficial effects of human milk  
22 that outweighed any possible potential effects of

1 methylmercury. Something clearly was happening in Iraq  
2 to allow these very high levels.

3 Now, with thimerosal, I mean, it's a different thing  
4 altogether. It's being injected. And so you're  
5 comparing quite a different media of injection here,  
6 which might not be good news for you. I mean, you're  
7 not giving it in human milk, so you might not get the  
8 protection that you would see there.

9 **DR. RAUB:** Dr. Bolger?

10 **DR. BOLGER:** I just wanted to comment on two things.  
11 One is, bear in mind that these estimates of relative  
12 sensitivity based on the Iraqi study are fairly  
13 uncertain. I mean, we only 81 subjects in there, and,  
14 in fact, the bulk of those children's mothers had body  
15 burdens well above 50 parts per million hair levels.  
16 So you only had several subjects in the low-dose range,  
17 of course, which is the dose range of concern for  
18 methylmercury in terms of fish-eating populations.  
19 And then, in terms of the indices of development that  
20 were measured in Iraq, delayed walking and delayed  
21 talking, when Dr. Clarkson's group looked at those  
22 endpoints in the Seychelles, they did not see that kind

1 of corresponding correlation. So, bear that in mind,  
2 that there are still some significant uncertainties in  
3 terms of how you measure development and what you're  
4 looking at.

5 **DR. RAUB:** Yes? You're up again.

6 **DR. RABINOVICH:** I'm not sure if everyone is still in  
7 the nap time. I'm just trying to understand the many  
8 issues that you're raising.

9 I think I've heard it at other meetings, but perhaps it  
10 should be stated here. What do we know about breast-  
11 feeding and intake through oral and exposure to a  
12 breast-feeding infant for methylmercury, ethylmercury,  
13 whatever you found?

14 **DR. CLARKSON:** The breast milk contains a fairly  
15 proportion of inorganic mercury. People exposed to  
16 methylmercury, certainly in Iraq and in fish-eating  
17 populations, breast milk is in both the methyl and  
18 inorganic. A great deal of attention has been played  
19 to the methyl and very little to the inorganic that's  
20 coming in breast milk. This may have some reverence,  
21 this thimerosal, really, because it also breaks down to  
22 an inorganic mercury. This is not -- To the best of my

1 knowledge, it has never been looked at very much from a  
2 health risk point of view, but inorganic mercury in  
3 breast milk is probably well absorbed. In adults, the  
4 absorption of inorganic mercury averages around 7  
5 percent. There's a range, but it averages about 7.  
6 Probably in suckling infants it's much higher, of the  
7 order of maybe 50 percent. The most divalent ions are  
8 absorbed to a much higher extent in the intestines of  
9 the immature infant.

10 So one has to worry, too -- This hasn't been looked at  
11 as to how the absorption of the inorganic might have an  
12 impact, for example, on kidney function. So to the  
13 best of my knowledge, it has not been looked at in any  
14 detail, not even with methylmercury.

15 **DR. RABINOVICH:** The environmental health people, if  
16 you could summarize briefly how you think differently  
17 about organic metallic, like methyl or ethyl mercury,  
18 and inorganic mercury in terms of health impact.

19 **DR. MAHAFFEY:** Well, our understanding of this, based  
20 on Swedish data and modeling a PDPK model that was done  
21 at EPA, is that both methylmercury and inorganic  
22 mercury can enter the mother's milk, and it depends, in

1 part, on what her own exposures are. If she has  
2 comparatively high seafood intake, she can be expected  
3 to have comparatively more methylmercury in the milk.  
4 It's known, too, that dental amalgams can contribute to  
5 the inorganic mercury level in the mother's milk.  
6 I was interested in Dr. Clarkson's comments about Dr.  
7 Amanzaki's work, which are found in the American  
8 Journal of Diseases of Children, Volume 130, October,  
9 1976, and I guess there must have been more infants  
10 than were written up, because this one only describes  
11 one infant who did remain well, but she was only  
12 evaluated for a short period of time, and they make  
13 specific reference to concern over what her longer-term  
14 effects might be.

15 So, I mean, you have to -- This is Amanzaki in the  
16 American Journal of Disease of Children, '76.

17 **DR. CLARKSON:** Well, we're in a better journal. We  
18 have one in the Journal of Pediatrics. Okay? So this  
19 is -- this has 15.

20 **DR. MAHAFFEY:** Okay. So there were additional ones.

21 **DR. DeROSA:** I just wanted to return to the comment  
22 about the exposure through breast milk, and there have

1        been some studies done, the Swedish study, in  
2        particular, that suggested a 50 percent distribution  
3        between the inorganic and the organic forms of mercury,  
4        that when they looked at the kids who were nursing that  
5        the relative proportion was 75 percent organic to 25  
6        percent inorganic because of the greater bio-  
7        availability, greater uptake of the organic form vis-a-  
8        vis the inorganic.

9        **DR. RAUB:** Dr. Plotkin?

10       **DR. PLOTKIN:** Well, since everybody's been  
11       extrapolating, I thought I might take a shot at it and  
12       ask the panel what they think of this. The only data  
13       we have, and, obviously, they're insufficient, are the  
14       five term infants from the Emory study who had a blood  
15       level averaging 2.3 micrograms. Assuming that they  
16       were 3 1/2 kilo infants, that means they -- and there's  
17       12.5 micrograms in hepatitis B, so they received about  
18       4 micrograms per kilo.

19       Now, at two months an infant could conceivably receive  
20       five times that. That is, 62.5 micrograms. Dr. Bolger  
21       seemed to say that there are no dose response data, but  
22       assuming what I guess is the worst case scenario, that

1 the -- you can multiply, that suggests that they would  
2 have a peak. That is, at two months, they would have a  
3 peak of 7 micrograms, assuming, of course, the factor  
4 of growth.

5 Now, is that extrapolation -- assuming that the Emory  
6 data are correct, is that way out of line, or does  
7 that, indeed, suggest that they would achieve blood  
8 levels of about 7 micrograms, which would translate, if  
9 I understood Dr. Clarkson, to about 1 or 2 parts per  
10 million in the hair?

11 **DR. CLARKSON:** I think it does. Can I show my thing  
12 again?

13 **DR. CLARKSON:** These are the data I used, which I got  
14 from Dr. Halsey, I think, by permission of the American  
15 Academy of Pediatrics, so it must be right. And  
16 obviously, those bodyweights are rather low. I used  
17 two of them: the three standard deviation one and the  
18 fifth percentile. These were the doses I was given  
19 from the vaccines; is that correct? 12.5 at birth and  
20 so on and so forth.

21 Now, if you go through the arithmetic on this, it's  
22 simple enough even for me to do it, you assume that 5

1 percent of this dose goes to the blood compartment, and  
2 that's mimicking methylmercury, I might add. And  
3 usually, distribution is complete in about three days  
4 in humans. Then you assume that the volume of the  
5 blood compartment -- Dr. Halsey, correct me if I'm  
6 wrong. You said 8 1/2 percent of the bodyweight,  
7 correct?

8 **DR. HALSEY:** At birth.

9 **DR. CLARKSON:** At birth, yeah. Well, I took it for six  
10 months, as well. Not being a pediatrician, I just did.

11 So if you do that -- Because I felt they're only  
12 numbers, you know, you can do the arithmetic better  
13 than I can -- you come up with blood levels shown on  
14 that last column -- Can you read that? -- of -- Well,  
15 not on that. That's the dose. Now, the blood levels  
16 you get are on the next slide, which I showed you this  
17 morning, and you can see that it's a small dose at  
18 birth. The yellow one is the smallest bodyweight, of  
19 course, the three standard deviation one. If you can  
20 read the white one, it's the fifth percentile. You can  
21 see that after the first vaccination, background levels  
22 in blood are about 1 part per billion, depending on

1 fish consumption and all that. Generally speaking,  
2 they're down there. You get a modest increase to less  
3 than five.

4 And then this decline here is simply due to the  
5 increase in bodyweight. I'm making that key assumption  
6 that there's no excretion whatsoever of mercury during  
7 this period, and that assumption comes only from animal  
8 experiments. We think we know the mechanism of that,  
9 but we don't -- and it probably should apply to humans,  
10 but there's no observations made yet on humans.

11 And I think this -- this discussion of vaccines might  
12 help us solve this problem, might be able to get some  
13 samples. Don't give me too many fecal samples at once,  
14 but we want to be able to get some samples that might  
15 solve this problem.

16 And then when you give the larger dose, the 62.5,  
17 obviously, there's a rather sharp increase, again a  
18 decline due to growth, and so forth. You can see this  
19 sort of pattern will eventually get you up into the  
20 20s.

21 Now, the regulatory guidelines are roughly for EPA  
22 around 5, 4 or 5. I think FDA is around 20. It's the

1 classic one we've had for ages and ages. WHO, as well,  
2 is around 20, about here. So that we just edge up and  
3 sort of go between the various guidelines on that.

4 It's a matter of what arithmetic you want to do, what  
5 assumptions you want to make about the bodyweight of  
6 the child, and how frequently the vaccines are given,  
7 and what's the mercury in the vaccines.

8 And my view is that it's the maximum level that  
9 determines the damage. Methylmercury is an  
10 irreversible poison. It knocks out the brain cells.  
11 So probably, it's not so much the length of exposure,  
12 it's the peak exposure that's really going to do the  
13 total damage. The Iraq dose response that the EPA used  
14 in their risk assessment was based on peak levels, not  
15 average levels, but peak levels. And so in this sense,  
16 it's the peak levels here I would imagine that are  
17 probably important to worry about.

18 And this is obviously a worst-case scenario. These are  
19 the lowest possible bodyweights. And I heard this  
20 morning that you're not even supposed to give a vaccine  
21 to an infant at 1.8 kilograms, and this is 1.8  
22 kilograms here. Okay? Thanks.

1       **DR. RAUB:** We just have a few minutes. There's one  
2 hand in back and then a couple down front here. We  
3 probably have time for about two or three more  
4 questions.

5 The gentleman in the back?

6       **DR. BERNIER:** My name is Roger Bernier from the  
7 National Immunization Program at CDC.

8 I wonder if we could get some more discussion about the  
9 application of these standards, because I think one of  
10 the things that characterized the policy-making around  
11 this episode was, I think, the perception or the  
12 interpretation of these guidelines as in some ways  
13 bright lines where there, in fact, was a violation of  
14 safe levels. And the insights that I'm getting from  
15 hearing you talk about these is very interesting  
16 because you're talking about these guidelines as  
17 starting points, as screening levels that you would  
18 then begin to investigate further. I guess it suggests  
19 to me that there's an art to the application of these  
20 guidelines.

21 And I wonder if you have ideas about, or from past  
22 experience, a protocol or a checklist for once you have

1 hit this screening level and you are now beginning your  
2 further investigation, what are the things to do. I  
3 mean, from other situations where you have experienced  
4 violations or things have occurred in excess, is there  
5 guidance that you can give in this art of applying  
6 these standards so that we can then judge what we are  
7 doing in the vaccine area and how we are doing as  
8 appliers of these standards?

9 **DR. MAHAFFEY:** If I could offer one comment. One of  
10 our concerns with our estimates for reference dose and  
11 mercury exposure is over what time period of both  
12 exposure and, in the case of methylmercury,  
13 developmental period these exposures are appropriate  
14 for.

15 When we did the report to Congress, there was a lot of  
16 back-and-forth discussion over what time period of  
17 exposure we should average mercury intake from fish.  
18 We had some daily exposures in there. We had monthly  
19 exposures in there, too. Certainly, the day-to-day  
20 variability in fish intake will produce a much higher  
21 range of exposure if you look at a one-day kind of  
22 intake.

1 At that point, we looked at 30-day intakes.

2 In listening to the experimental animal panel talk  
3 about the importance of an intermittent high-dose  
4 exposure on C and S development, at least in animals, I  
5 personally began to wonder if our 30-month period was  
6 too long. I don't know what the appropriate period  
7 really is, but it has been the topic of a lot of  
8 discussion.

9 The reference doses are intended to be a level that's  
10 thought to be safe over a very long period of exposure,  
11 and clearly what that relevant period is can be, in  
12 part, determined by the what the endpoint is you're  
13 trying to look at. If you're looking at  
14 carcinogenicity, clearly a longtime period of exposure  
15 is the period of greatest interest. With  
16 methylmercury, we know that there are developmental  
17 windows of importance.

18 I think with this, as others have pointed out, this  
19 peak exposure that happens is something that is  
20 fundamentally quite different from the usual  
21 application of reference doses, and I would think the  
22 kinetic information has got to be very important here

1 because it may suggest that the risk is higher than  
2 what might be assumed from just applying the reference  
3 doses, or the MRL.

4 On the other hand, additional kinetic data may show  
5 that ethylmercury is a sufficiently different compound  
6 in its metabolism that the RfD, or MRL for  
7 methylmercury, may not be that relevant, but, in the  
8 interim, risk managers will have to make some  
9 decisions.

10 **DR. GREENBERG:** I think this has been a great  
11 discussion, but we should take a break now. You can  
12 continue this discussion in the hallways, and we'll be  
13 back here at 3:30 for the last session.

14 (RECESS FROM 3:00 P.M. TO 3:34 P.M.)

15 (END VOLUME I - DAY ONE)

16 **SEE VOLUME II - DAY ONE)**

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C E R T I F I C A T E

G E O R G I A )

FULTON COUNTY )

I, Pamela T. Lennard, being a Certified Court Reporter in and for the State of Georgia, do hereby certify that the foregoing, consisting of pages 1 through 221 (VOLUME I - DAY ONE), inclusive, was reduced to typewriting by me personally or under my supervision and is a true, complete, and correct transcript of the aforesaid proceedings reported by me.

I further certify that I am not related to, employed by, or attorney or counsel for any parties, attorneys, or counsel involved herein; nor am I financially interested in this matter.

WITNESS MY HAND AND OFFICIAL SEAL, this 5th day of September, 1999.

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Pamela T. Lennard, CCR-CVR  
CCR No. B-1797

[SEAL]