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ATDEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR FOOD SAFETY AND APPLIED NUTRITION

FOOD ADVISORY COMMITTEE

METHYLMERCURY

Tuesday, July 23, 2002

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GUEST SPEAKERS

Mr. Harvey Clewell
Dr. Christopher DeRosa
Ms. Caroline Smith DeWaal
Dr. Philippe Grandjean
Dr. James Heimbach
Dr. Joseph Jacobson
Dr. Penny Kris-Etherton
Dr. Gary Myers
Dr. Susan Schober

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C O N T E N T S

C O N T E N T S(Continued)

P R O C E E D I N G S

Welcome and Introductions

DR. MILLER: Good morning. I am Sandy Miller and I am serving as the Chairman of the Food Advisory Committee for the Center for Food Safety and Applied Nutrition. I would like to welcome you all to this meeting, which was called in order to help the Center develop a policy for methylmercury in food.

The Center has developed a number of questions which they want the committee to consider, and these will be discussed in just a few moments.

Let me just go into the agenda. Let me just see if I can get some ground rules in place. This is a very tightly packed agenda. If we are going to be done anytime within the next month or two, we are going to have to stick to the exact times that have been assigned by the secretary. These generally have been determined by the speakers themselves, but in some cases, in order to finish the agenda, the times have slightly changed.

Nevertheless, the important thing is that exactly on time, I will ask you to step down. I will try five minutes before the end of your time to remind you that there is five minutes to go, but it is really important that we stick to the time.

I know this is an issue of some concern and a great deal of passion to a lot of people, and it is of vital importance to us, but we want to be fair to everybody, the times must really be kept.

Secondly, just to indicate the basis for which the committee is operating, it is the function of this committee to look at these questions which we will be asked on the basis of the science. Our recommendations are individual recommendations to the Center to be based entirely on that issue.

Policy determinations are complex and they involve things that are equally important to the science, but are different. This committee is not designed to deal with those issues, so I am asking you all to try to focus your attention on the issues concerned with the science and the science only.

Let me introduce to you Cathy DeRoever, who is the Executive Secretary of the Food Advisory Committee, who will talk about some housekeeping issues.

MS. DeROEVER: Thank you, Dr. Miller.

Good morning. I would like to welcome all of our members and our temporary voting members. Thank you very much for being here today. Before I do actually the administrative announcement, for the record, I want to

announce that we have appointed several temporary voting members.

Conflict of Interest Statement

The authority to appoint such members is granted to the Center Director, and I have letters for the temporary voting members that state: By the authority granted under the Food Advisory Committee Charter, I appoint Dr. Aposhian, Dr. Friedman, Ms. Halloran, Dr. McBride, Dr. Nordgren, and Dr. Scherer as temporary voting members of the Food Advisory Committee for the July 23rd through 25th, 2002 meeting on methylmercury

The letter is signed by the Center Director, Center for Food Safety and Applied Nutrition, U.S. Food and Drug Administration, Mr. Joseph Levitt.

Second, also for the record, all members and temporary voting members have been screened for financial conflicts of interest. Upon review of the FDA Form 3410, which is the financial disclosure report for special government employees, we have determined that no financial conflicts exist.

Similarly, we have asked all our guest speakers to complete a financial interest and professional relationship certificate for guests and guest speakers to identify any potential conflicts.

We have not received all of those forms, but for the record, there are two that I would like to mention. Dr. Heimbach has had a relationship with the seafood industry, and Dr. Kris-Etherton, who will be speaking I believe it's tomorrow, has a relationship also with the seafood industry.

Moving on to the administrative matter, for the people at the table, in your notebook is a menu that we are going to ask you if you would like to have lunch, we have tried to overcome some past problems we have had with respect to timing, so if you would take a moment and complete it, the staff will collect it and your lunch will be ready, hopefully, when we break. If this works well, we will try it again for Wednesday and Thursday, but I will appreciate your feedback on that.

With that, I turn it back to Dr. Miller.

DR. MILLER: Thank you, Cathy.

To open this session of the Food Advisory Committee, Mr. Joseph Levitt, who is Director of the Center for Food Safety and Applied Nutrition, has some opening remarks.

Opening Remarks

Joseph A. Levitt

MR. LEVITT: Good morning. Again, my name is Joe Levitt. I am Director of the Center for Food Safety and

Applied Nutrition. I am pleased to welcome all of you here for a meeting of the Food Advisory Committee.

This is my first visit with the committee since you were reconstituted. I was on vacation when there was a meeting earlier this spring. I welcome Dr. Miller, who is chair of our committee. Simply no one has more experience in the broad issues facing our Center than Dr. Miller given his past experience at the Agency and his work on many National Academy of Sciences committees.

I also will look forward to working with the committee as a whole and its many subcommittees over the coming months and years, and in the fall, I will look forward to providing you on a day when we have a less intense agenda with an overview of our Center's activities and on engaging your advice on a number of important scientific and public health issues, which brings me to this week's meeting on FDA's Consumer Advisory regarding methylmercury and seafood consumption.

We consider this issue to be a very important public health issue. Indeed, I can't think of anything more important than ensuring the health of pregnant women and their unborn children.

That is why we went to great lengths to assemble such a distinguished committee. For those not familiar with our committee structure, we have included here members

of our standing Food Advisory Committee, members of our new Subcommittee on Food Contaminants, and additional scientific experts in specialties needed for the methylmercury issue that we did not already have.

This includes medical experts in pediatrics and neurology, as well as additional experts in developmental psychology and risk communication.

Finally, I want to thank Jean Halloran of Consumers Union for serving as our consumer rep given that our standing consumer rep was not here. I am not sure I see her yet, but we will thank her in advance of her arrival.

Again, I want to thank everybody for taking the time from your very busy schedules to address this subject.

This issue methylmercury in fish has a long history dating back to the 1970s. This includes industrial poisonings in Japan and Iraq, major studies being conducted in geographical areas of heavy fish consumption, steps being initiated by both the FDA and the Environmental Protection Agency, as well as a number of risk analyses and data gathering exercises.

You will hear about all of this and more over the next three days I can assure you. The critical point of departure for this week's discussion is a report issued by the National Academy of Sciences on July 11th, 2000. The

report was actually directed to EPA under the rubric of reducing environmental pollution by this relevant to FDA regarding commercial seafood consumption was readily apparent.

Therefore, after the National Academy of Sciences' report, we, at FDA, undertook a very extensive process to examine the risks of methylmercury in commercial seafood and to determine what advice to give consumers at the national level.

We consulted with many of the same people and organizations that you will hear at this meeting. We conducted a series of focus groups with consumers to examine communication style and format that any new advisory would have, and we consulted with EPA, which issues advisories to states for recreationally caught fish.

I personally led this outreach effort and I participated in every or nearly every meeting with outside groups. I also met regularly with our internal staff on a regular basis. The culmination of this effort was an updated consumer advisory that FDA issued in January 2001 with a small revision in March a couple months later.

Let me now summarize the advisory itself. The consumer advisory was addressed to pregnant women and women of childbearing age who may become pregnant. In short, the advisory has two main parts. The first part says to avoid

eating four kinds of fish with the highest levels of mercury, namely, shark, swordfish, king mackerel, and tilefish, avoid these completely if you are in that category.

No. 2. Eat 12 ounces per week of a variety of other fish including shellfish, canned fish, smaller ocean fish or farm-raised fish. Just be sure to pick a variety of different species.

I tend to summarize this advisory to say avoid the top four fish and eat the rest in moderation.

Now, in issuing this advisory, FDA also put on our web site our written rationale for the advisory and data tables showing levels of methylmercury in different species of commercial fish, so the public could see how we reached the conclusion we did.

We followed the issuance of the advisory with an extensive outreach campaign and were able to get our message into a number of newspapers, magazine, and other information outlets.

When we issued this advisory in early 2001, it was our genuine belief that if women conscientiously followed this advisory, based on knowledge of methylmercury levels in fish and consumers' fish consumption levels, that these women would be protecting their unborn children from harm due to methylmercury. That was our goal.

But I can tell you, a year and a half later, the subject remains controversial and I will tell you quite candidly that a number of persons and organizations still feel that we fell somewhat short of the mark. That is why we are here.

We want American women to have the best advice possible and for that advice to be arrived at in an open and transparent way. At the time that we constructed our advisory a year and a half ago, CFSAN did not have at the time the benefit of our Food Advisory Committee. We were in the process of recharging and restructuring it, and so forth.

So, we assembled the advisory ourselves using the best information we had and the process that I described, but now that we have reconstituted this advisory committee and it is fully functioning, we wanted to bring the issue to you. We look forward to a full airing of the issues, ultimately focusing on whether, after everything is considered, the advisory is as strong as it needs to be to protect public health.

Now, over the next three days, you will hear a wide range of views on this subject. Your job is first to listen critically to the whole story that will be presented to you over the next three days. You will hear, starting with the representative from the Academy that issued the

report. You will hear directly from a number of researchers who have conducted the key studies.

You will hear from state and federal officials, from physicians, from consumer groups, from industry representatives. Finally, you will hear from experts in our center who will try to explain how we arrived at the conclusions that we did.

Then, we will stop and you will have your discussion. We want your best thinking and advice on our advisory on whether it is adequate in its present form or whether any adjustments need to be made.

Now, let me go through the specific charge.

This will be circulated and everybody will have copies of this if they don't already. It will be coming around shortly.

[Slide.]

The charge to the committee, I have kind of a long version and a short version. The long version says:

The committee is being asked to evaluate, in light of all the relevant information about potential consumption, exposures, population body burden, hazard and consumer messages, whether the Agency's Consumer Public Health Advisory on Methylmercury is adequate to protect the health of those who follow that advice.

When I read that, I said that covers everything, but let's say it a little more simply.

[Slide.]

To put it more simply, does the FDA advisory provide adequate protection for pregnant women and women of childbearing age who may become pregnant? That's the bottom line question. If not, what changes are needed and why? If yes, are there nevertheless enhancements to the advisory that would make it easier and more effective for women to follow it?

Now, to help answer this general charge, we have framed it in five questions.

The first question says: Has the Agency adequately addressed and appropriately considered all the relevant factors and information that bear upon the elaboration of a consumer advisory on fish consumption? Are any factors not relevant? Are there additional factors that should be relevant? In other words, have we considered the landscape.

No. 2. Focusing on the first part of the advisory, should the advisory have specifically advised pregnant women to avoid any other species not specifically mentioned, and if so, what would be the scientific rationale?

I will tell you as you will hear, that the species most commonly mentioned would be fresh tuna is the fish you will hear a lot about, whether it ought to be included here or not. So, we want that to be talked about.

No. 3. In the second part of the advisory, should the Agency issue a fish listing as an adjunct to the advisory to clarify what is mean by "variety of fish?"

As we have gone back and looked at the advisory with hindsight, we knew what we meant, but have we provided enough information on how to eat the appropriate variety of fish, so that women are adequately protected. We would like advice there.

No. 4. You will hear a lot about FDA and EPA, so we ask the question: Should the Agency revised our advisory to make explicit that the 12 ounces per week includes all sources of fish, both recreational and commercial, so there is a better nexus? There may be additional ways you consider how we and EPA can better be sure that we are connected, we have our web sites joined, and so forth, maybe there are additional ways.

Finally, a subject of monitoring. Should the Agency increase its monitoring of methylmercury in commercial fish in order to keep this advice current? When you go through the data tables, you will see that some of the species have lots of samples, some have very few

samples associated with them, and the question of monitoring and importance of that comes up, so we would like your advice on that.

Let me conclude. Dr. Miller asked that I describe for you two things: Number one, why you are here, and, two, what FDA needs from you over the next three days. I hope I have done that.

I also hope that I have conveyed that we are truly open and indeed want your best advice whether you agree with us or not. You will see I believe, as I did, that there is a wide range of strongly differing views about methylmercury in fish. It is an emotionally charged issue.

There is also a long history of scientific debate about this issue that will not likely end with this meeting although it would be nice. Our collective challenge, therefore, during the next three days will be to rise above any such divisiveness. We need to do what is best for the American consumer, in this case, American women and their offspring. They certainly deserve no less.

Thank you very much. I will try personally to stay for as much of the meeting as I can although I am sure a couple times I will get pulled out for different issues.

Again, thank you for your time. You will have a fascinating three days, I can assure you, but most

importantly, we hope that you will help us move and advance this issue in a way that will be best for American women and their children.

Thank you again very, very much, and thank you, Dr. Miller, for chairing the meeting.

DR. MILLER: Thank you, Joe.

Introductions

Before we proceed, let me take this opportunity of having the various members of the committee introduce themselves, at least for the record, so we know you are here.

We will begin with Dr. Scherer.

DR. SCHERER: Cliff Scherer, Cornell University, Department of Communications. My specialty is risk communication.

DR. NORDGREN: Dick Nordgren. I am a pediatric neurologist from Dartmouth Medical School.

DR. McBRIDE: Margaret McBride. I am a pediatric neurologist from Rochester, New York, and Akron, Ohio.

DR. FRIEDMAN: Sarah Friedman from the National Institute of Child Health & Development, one of the NIH institutes. I am a developmental psychologist.

DR. RUSSELL: Rob Russell. I am Director of the Human Nutrition Research Center at Tufts.

DR. MONTVILLE: Tom Montville, Professor of Food Science from Rutgers, The State University of New Jersey.

DR. FULLER: Marion Fuller. I am the Director of Food Safety for the Florida Department of Agriculture and Consumer Services.

DR. FISCHER: I am Larry Fischer, Director of the Institute for Environmental Toxicology at Michigan State University.

DR. HOTCHKISS: Joe Hotchkiss from the Department of Food Science at Cornell University.

DR. LEE: Ken Lee, Ohio State University, Department of Food Science, Professor and Chair.

DR. KUZMINSKI: I am Larry Kuzminski, a retired Vice President of Technology from Ocean Spray, had previous positions to Ocean Spray that included officer positions with the Kellogg Company and tenure professorship at University of Massachusetts.

DR. MILLER: I am Sandy Miller and I am associated with the Center for Food Nutrition Policy at Virginia Tech University.

MS. DeROEVER: Catherine DeRoever, FDA.

DR. BUSTA: Frank Busta. I am a Professor Emeritus, Department of Food Science and Nutrition, at the University of Minnesota.

DR. ACHOLONU: Alex Acholonu. I am from Alcorn State University in Mississippi. I am a Professor of Biology and my specialty is epidemiology of diseases.

DR. DICKINSON: Annette Dickinson, Vice President for Scientific and Regulatory Affairs with the Council for Responsible Nutrition.

DR. DWYER: Johanna Dwyer, Assistant Administrator for Human Nutrition, Agricultural Research Service, USDA.

DR. SHANNON: I am Michael Shannon. I am a pediatrician and toxicologist at Children's Hospital and Harvard Medical School in Boston.

DR. APOSHIAN: I an Vas Aposhian from the Department of Molecular & Cellular Biology and the Department of Pharmacology at the University of Arizona. My research interests have for many years been the toxicology of heavy metals including mercury and arsenic.

DR. MILLER: Thank you all. There are still a couple of members of the committee that have not yet arrived. When they do, we will have them introduce themselves.

Let me make a request, that when you speak, try to speak into the microphone since there is a record of this meeting being kept.

Our first speaker is Dr. Joseph Jacobson, a member of the National Academy, Committee on Methylmercury. Dr. Jacobson is from Wayne State University.

Dr. Jacobson.

National Academy of Sciences Report on the Toxicological Effects of Methylmercury

Dr. Joseph Jacobson

DR. JACOBSON: First of all, I want to apologize. I am not quite sure how I got to the 20 minutes, but in reviewing this morning, I really am going to need 30. We are a little ahead, so hopefully, that won't be a problem for your schedule.

DR. MILLER: Okay, as long as we stay within the schedule, the exact moment.

DR. JACOBSON: I am a developmental psychologist and I am going to be giving you an overview of the history behind the constituting of the NAS panel, as well as some of the logic and thinking that went into the process of the conclusions that we reached in our report.

Vas Aposhian was a member of the panel. He is here, so he can correct me if I get some of the details wrong.

[Slide.]

Obviously, everyone here I am sure is familiar with the fact that prenatal exposure to methylmercury can

have very serious developmental consequences for the central nervous system was first established in the Minamata incident in Japan, that led to some of the more severe deficits that were seen at the very heavy levels of exposure in that population.

[Slide.]

And then, of course, the second famous mass poisoning was in Iraq in the early 1970s when seed grain that had been contaminated with the methylmercury fungicide was used to bake bread because there was drought and the infant who were born to mothers who ate the contaminated bread while they were pregnant showed very similar severe neurological problems.

One important difference between the two episodes as that in Iraq, a group of researchers from the University of Rochester went in and did systematic assessments of a large number of the infants who were exposed, very systematic developmental assessments, and so we had, not just the qualitative descriptions, but also some reasonably semi-quantitative data that risk assessment could be based on.

[Slide.]

EPA, when it did, not the most recent risk assessment, but the one before that, used the Iraqi data as the basis for the risk assessment, and the developmental

endpoints that they used were developmental milestones - age of walking, age of talking, which were affected by the very heavy exposure levels in this population.

The EPA Iraqi risk assessment was the first to use a benchmark dose analysis for purposes of risk assessment. Prior to that, the method used was the NOAEL, the No Observed Adverse Effect Level method, which tended to be based on animal studies where different groups of animals would be exposed at different levels, and the lowest level at which no adverse effect was seen was the one that was used for the EPA reference dose, the reference dose being an estimate of the average daily intake at which you wouldn't find adverse effects.

When EPA and other agencies began to move to human data, we got the increasing popularity of the benchmark dose statistical assessment, which doesn't look for discrete groups, and, of course, in human exposures, you don't get discrete groups, people tend to be exposed over a broad range of exposures, and the benchmark dose analysis uses the full range of exposures and the outcomes associated with those exposures to arrive at a statistically driven estimate of the level where you might not see an adverse effect.

To do the benchmark dose analysis, you have to start out by taking a cutoff. Well, first of all, you have

to start out by picking an endpoint, and I will talk later about the choice of endpoints that the NAS Panel considered based on the data that were before us, but you have to pick an endpoint.

Once you have that endpoint, you have to pick a cutoff, and the cutoff represents the level at which you are saying the child is doing very poorly and we become very concerned. On an IQ test, we will often pick the level of 70, the borderline for mental retardation, and we will talk about 70 as the cutoff, that is, 70 as the level of poor performance that we are trying to prevent an increased incidence of.

So, we take an endpoint that methylmercury increases the incidence in the population, an endpoint where methylmercury makes it more likely that we are going to get a bad effect, and we pick a cutoff, and we say we want to make sure that we do not appreciably increase the number of children who are performing at that level just by virtue of the fact that they were exposed to methylmercury.

The benchmark response is our criterion for how much of an increase we are willing to tolerate. Let's say we are willing to tolerate a deficit of 70, an IQ deficit of 70, and we are willing to tolerate an increase of 1 percent or 2 percent.

Typically, we don't want there to be enough methylmercury exposure in the population that the incidence of mental retardation is increased by 5 percent or 10 percent. So, the benchmark response is our decision.

These are all policy driven, what level of performance is the cutoff, what level of performance are we really trying to prevent an increased incidence of, what benchmark response are we willing to tolerate how much of an increased incidence of poor performance are we willing to tolerate, and once we have made those decisions, we use the dose-response data from our studies to plot a dose-response line, usually, it is done as a straight line, and that dose- response data lets us determine the dose, the level of exposure at which we get that increased incidence that we are very, very eager to prevent.

So, this is a statistically driven analysis. We use the full range of the dose-response data to derive a benchmark dose, and then we set 95 percent confidence limits around that dose, and the lower 95th percentile is called the BMDL, the lower limit of the benchmark dose.

That is the point of departure that EPA used in its Iraqi risk assessment, as well as in the more recent risk assessment to derive the RfD. What I am leaving out of this is once you get the BMDL, once you get the lowest level at which we expect to see a deficit in the normal

population, then, you add the uncertainty factors that I am sure this group will be considering in more detail later on.

[Slide.]

As I said, the Iraqi data were used in the initial methylmercury assessment by EPA, but there were several problems with using the Iraqi data, and those included the fact that the developmental milestones, age of walking, age of talking, are fairly gross endpoints. They are not very sensitive, and they are not very predictive of how a child is going to do later on.

They were used because they were the best that was available using human data. The alternative was to extrapolate from animal data, but humans and animals will often metabolize metals differently, and so the feeling is that if we go with human data, there are some advantages to that.

The other major disadvantage with the Iraqi data was that the exposure was so high, that there were very few individuals in that sample who were exposed in the range at which we get exposure in the general population.

So, we were plotting a dose-response curve and then extrapolating down to apply to our population in a range at which there were very few datapoints.

So, although from some perspectives, the Iraqi risk assessment represented a real advance from a scientific point of view, there were really very serious problems in using it to make inferences for contemporary exposure, the other being, of course, that an acute exposure from seed grain is not necessarily going to have the same kind of damage as a chronic exposure from fish over a long period of time.

As a result, NIEHS, the National Institute of Environmental Health Sciences, funded two very large and very well-designed, prospective longitudinal studies of prenatal methylmercury exposure that started during the early 1990s.

One was in the Seychelles Island in the Indian Ocean, the other in the Faroe Islands in the North Sea. Those locations were chosen because they had populations where there were people who ate a lot of fish, and so you could get--and it is always optimal in these kinds of samples--to take a population where there is a broad range of exposures, in other words, you are going to get the clearest picture if you can see the full dose-response curve.

There still was good overlap with the exposures that we get in the U.S. population, but there was a broader range, and so that made those two populations optimal.

[Slide.]

The Seychelles Islands was the first to report effects, and the first effect that they reported came from a pilot study. It's actually rather large by my standards for a pilot study, and this was 217 children who were assessed at age 5, and they actually, mainly had very low exposed children and heavily exposed children.

They assessed 9 developmental endpoints, and I am showing them 3 of them here, but actually, they found statistically significant associations between prenatal methylmercury exposure and adverse outcome on 4 of their developmental endpoints.

One was the General Cognitive Index, which is like an IQ score for pre-schoolchildren from the McCarthy scales of children's abilities, which is an IQ-type test for pre-schoolchildren. Another was on the Perceptual Performance subtest of the McCarthy, visual-spatial function, preschool language, and Auditory Comprehension was the fourth one that is not shown.

What was unusual about this report was that the investigators themselves, after reporting the data, tended to discount it, and they discounted it on two grounds - one, that there were 4 outliers, which when they were dropped from the analysis, the results were no longer statistically significant, and the other was that they had

not measured a full range of potential confounding variables, particularly social class, and had not controlled for them.

The Panel reviewing these data raised questions about whether they should have been discounted. Dropping outliers, not all statisticians agree that is the best way to handle outliers. A lot of statisticians feel they should be recoded. The social class, we did not think was necessarily such a serious problem here, because methylmercury tends to be more concentrated in more expensive fish, and, if anything, it is likely that the more middle class children got the heavy exposures.

But again, this is a pilot study, and these are tentative data, and no one would do a risk assessment based on these data, but they were the first indication from this more recent series of studies of adverse effects.

[Slide.]

However, when the Seychelles group, which is the University of Rochester group, assessed the main study, the full cohort several years later, at the same age, that is, at age 5 1/2, they found no evidence of adverse effect.

[Slide.]

I have a slide here to demonstrate there just was no relationship between exposure and outcome. I mean, you

know, you can look and look and look, but there is nothing going on in these data of this second main cohort.

[Slide.]

The endpoints they assessed tended to be relatively global endpoints, that is, again the McCarthy General Cognitive Index, preschool language tests, tests of academic achievement as opposed to what we call narrow band, domain-specific tests where a test might look in great detail at one aspect of cognitive function, such as sustained attention or vocabulary or visual-spatial reasoning, and so forth.

Here, the Seychelles group tended to use more global tests and saw no adverse effect.

[Slide.]

They also used maternal hair as their measure of prenatal exposure. Mercury is excreted in the hair, and so if the mother has long hair, which most of the women in this population do, and you get a sample of her hair after she delivers--and hair we know grows at a rate of about 1.1 cm per month--you can take the hair, you can estimate when during pregnancy the mercury was excreted into the hair, and get a very accurate retrospective picture of the mercury intake during pregnancy.

[Slide.]

So, as I said, Seychelles, age 5 1/2, main study, no evidence of adverse effect, not even a hint or a suggestion in the data.

By contrast, we had the Faroe study at age 7, which did not use global tests, they used more narrow band, domain-specific tests, and they reported I think it's out of 20 outcomes, they found adverse effects on 8 of them, and these were actually in many domains.

Even though they were domain-specific tests, adverse effects were found across the full range of cognitive and neuromotor functioning including fine motor function, finger tapping, sustained attention, short-term memory as assessed in the digit span test, vocabulary as assessed in the Boston Naming test, and verbal learning and memory as assessed in the California Verbal Learning test.

The publication of these two studies, as I said, both well designed, both very large samples, exposure levels, very similar, presented quite a quandary both to scientists and regulators - how is it possible that you can conduct two large-scale comprehensive, state-of-the-art studies and come up with such absolutely contradictory findings.

One of the first responses to the appearance of these two sets of contradictory data was that NIEHS and EPA, and other agencies, ATSDR, Chris DeRosa was involved

in this who is here today, convened a workshop in Raleigh, North Carolina in 1998, where there were 50 scientists assembled. Larry Fischer was one of the scientists on that panel. We spent 2 1/2 days intensively scrutinizing these two studies, and we brought in the investigators, and, boy, I would not have liked to have been in their shoes for the close questioning, detail by detail, that these people underwent.

But we learned a lot. We learned a lot about the studies at that time, and the question, as I said, from a scientific point of view, is how can you have two large-scale studies come up with absolutely contradictory findings.

[Slide.]

At the end of the 2 1/2 days, having considered the data, the panel concluded that there were several differences in exposure and design that could explain how one study concluded there were adverse effects and the other study concluded no adverse effects.

One had to do with biomarker of exposure. As I mentioned, the Seychelles study used maternal hair mercury. I didn't mention the Faroe study, in their initial reports, used cord blood mercury. Now, cord blood mercury reflects intake during pregnancy during the last, I think it is 12 weeks or the latter part of pregnancy, and that is the

period when we get a lot of neuronal proliferation differentiation and brain development that might well be involved in the kind of endpoints that were being assessed in these studies.

So, it was plausible to say maybe the Faroe's group was measuring mercury at the right time to see the problem. However, subsequently, the Faroe's group, they also had the hair samples, they just hadn't analyzed them yet, analyzed the maternal hair and looked at it in relation to these developmental endpoints, and found the same adverse effects as they had found with cord blood, so the first theory which seemed to explain the differences kind of fell by the wayside.

The second was that global tests were used in the Seychelles, domain-specific tests in the Faroes. In retrospect, that doesn't seem all that convincing to me, because the Faroes group used the domain-specific tests, but found adverse effects across a broad range of domains, so the global tests, in my view, should have picked up. The narrow band tests are important if the deficit is only in one or two narrow domains, but it is clear from the Faroe's data that it isn't.

So, in retrospect, that one, I think we should have not put as much stock in as we did at the time. The age point, 5 1/2 years, is not a good time to do

developmental testing because it is a period of rapid brain growth, rapid cognitive reorganization, and relatively subtle neurotoxic effects are not likely to show up.

The Faroe's group, I think picked a better age point, 7. Once children have gotten past that developmental period, they usually perform in ways that are more stable and reliable over time.

Then, a fourth difference was the source of exposure. Both populations ate a lot of fish, but in the Faroe's, they also get a lot of methylmercury exposure from whale meat, and the difference in the fish, it is a low level chronic exposure, the woman is eating a little bit every day.

The whale meat, the methylmercury is much more concentrated, and they will beach the whale, there will be a big party, there will be splurging on whale meat, so to speak, and you could get some very heavy doses that perhaps could explain why you might see the adverse effects in the Seychelles, and not in the Faroes.

The fifth difference, that is not up there, is that the Faroes were heavily exposed to PCBs, which is a ubiquitous environmental contaminant, and there are two concerns about PCBs that you have to understand.

One is that it is possible, since you get PCBs from fish and methylmercury from fish, it is possible that

we have confounding. It is possible that the same children who get heavy methylmercury exposures, also get heavy PCB exposures, and that where you think you are measuring methylmercury, you are really measuring PCBs. That is one possible problem with the PCB exposure.

A second possible problem is that there may be synergism between the PCB and methylmercury exposure, that is, being exposed to methylmercury when you are also at the same time being exposed to PCBs may make the methylmercury more toxic. There is no good mechanism that has been hypothesized as to why the synergism would exist, but it certainly is possible in theory.

So, basically, these differences between the two cohorts allowed the 50 scientists in the Raleigh meeting to come up with an intellectually very satisfying understanding about why one well-designed study would lead to one set of results and another two, a very different set of results, but it presented no relief to the regulators who these are the data they have, and they have to one way or another make sense of them and come up with some criteria and recommendations.

Around this time, EPA was eager to set up some new rules to regulate emissions from coal-fired utility plants in the Midwest, and methylmercury is a major pollutant from that source.

They tried to issue the regulations and were blocked by congressmen from West Virginia and Ohio, and then the resulting battle in Congress led to a directive to NAS to convene an expert panel to try to look more carefully at the data and from a regulator's point of view, do a better job than the Raleigh group and come up with something that could be useful from a regulatory point of view.

[Slide.]

That is how the NAS panel was convened with representatives from a broad range of relevant disciplines, epidemiology, developmental psychology, statistics, methylmercury chemistry, and so forth.

[Slide.]

One key difference in our deliberations, in the deliberations of the NAS panel, over what had come before in the Raleigh panel, was that in the NAS panel, we considered the results from an earlier study, from a study that was conducted in the late 1980s in New Zealand, which the Raleigh panel was instructed not to pay attention to because it wasn't published.

Well, after the Raleigh panel meeting, some of it became published, and we considered it in the NAS panel. Although it is not as large a sample, I think there were about 230 children, not as well designed in terms of

controlling for confounders. There was some control, but not as comprehensive. It is actually quite a good epidemiological study as these studies go.

What is interesting about it is that in terms of the sources of exposure and the design of the study, it is very similar to the Seychelles study, that is, the methylmercury was measured in the mother's hair, the children were assessed at about the same age, it was age 6 rather than age 5 1/2, the developmental endpoints were very many of the same global IQ and achievement tests, and so forth.

The difference was that the New Zealand study found adverse effects using the same exposure measures, the same research design, essentially the same research design as the Seychelles, they saw adverse effects.

In epidemiological studies, oftentimes what you have to do is go with the weight of the evidence.

Actually, let me put that off, because that point will be a little bit easier to make toward the end.

[Slide.]

So, basically, when we included the Seychelles pilot data and the New Zealand data, these differences that we thought had explained why we are seeing effects in one study, and not in the other, fell by the wayside.

We are seeing adverse effects with cord blood, mercury, and maternal hair mercury in multiple studies. We are seeing them on global tests, not just on narrow band tests. We are seeing them at age 5 1/2 and 6, and we are seeing them in populations where the exposure is just from fish.

PCBs, we don't know what the PCB exposures are in New Zealand, but there is no reason to expect there to be particularly high levels of exposure in New Zealand.

DR. MILLER: Dr. Jacobson, we have about five more minutes.

DR. JACOBSON: I will just try to say very briefly what the other slide was going to show, which has to do with the confounding of PCBs and methylmercury in the Faroe study. There were four endpoints which we shown on the slide where methylmercury affected the endpoint and PCBs did not. There were four where both methylmercury and PCBs affected the endpoint, and it was very difficult to tease apart that difference, and if people have more questions about it, I will try to explain that in greater detail.

Basically, once we see that these factors do not explain the differences between the two studies, you are left with the question, who could explain the difference between the two studies.

Well, one conclusion that we came up with on the panel was that we think that there is an issue of power. Now, when you have samples of 700 and 900 children, it is kind of funny to talk about power, because that would seem to be an adequate sample size to detect anything.

[Slide.]

There are two factors. First of all, much of the effect is going to be seen above 15 parts per million in maternal hair. We have got lots of cases at the lower end, but when you think about power, power is going to be weakened in these studies--this is the Seychelles data--even in a study of 700 children when you have a limited number of children whose exposure is in the upper end of the distribution where most of the effect is going to be seen, so there may have been a power problem from that point of view.

[Slide.]

Then, we took the raw regression coefficients that had been reported in the studies and transformed the standardized regression coefficients to try to get a sense for the magnitude of the effects, and what we find is that the magnitude of a lot of these effects is very, very small, so even very large samples may find it difficult to detect some of these very small effects.

[Slide.]

The other issue in an epidemiological study is there are many uncontrolled factors, there are many possible unmeasured confounders. We find this in the lead literature, the PCB literature, these other exposures where many studies have been done. You can have a well-designed study that fails to detect an effect that is seen in study after study.

The reasons are probably that in many populations or in any given sample, there may well be unmeasured factors that you are unable to control for because it doesn't occur to you that there could be confounders, and that is basically why you have to go with the weight of the evidence.

The basic conclusion in the NAS panel was even though one very well-designed study clearly failed to find effects, one very well-designed study did, one quite well-designed study did, and even the Seychelles pilot gave some indication, so the weight of the evidence seemed to be pretty clearly in the direction of adverse effect.

[Slide.]

When you do the benchmark analysis, you have to figure out, the way the methodology works is you have to choose a developmental endpoint that is going to be your guide, that is going to be the one that you do your statistic analyses based on.

Some people argue it should be the most sensitive endpoint, that is, the endpoint at which you see an effect at the lowest level of exposure. If we had recommended the most sensitive endpoint to EPA, we would have gone with the New Zealand data because effects were seen at the lowest levels in the New Zealand study.

We felt that since it was not a well-designed study, it had not had as extensive peer review, it was not as large a sample, that we would do better going with the Faroe study, which did show adverse effects at somewhat higher levels of exposure.

Based on methylmercury maternal hair, the endpoint at which we saw effects at the lowest doses was the Boston Naming Test, it's a vocabulary test, so that was the endpoint that we decided to go with in terms of recommendation for EPA for its risk assessment benchmark dose computation.

Thank you.

DR. MILLER: Thank you very much.

Comments, questions from the committee? Yes, Dr. Russell.

Questions of Clarification

DR. RUSSELL: I was wondering, is another possible explanation for the differences that the diets eaten in these various areas differ in other components

that could affect the absorption or the bioavailability, if you will, of the methylmercury? In other words, if the rest of the diet that was eaten with fish is vastly different from place to place, could that affect the amount that is absorbed?

DR. JACOBSON: In principle, yes. I am not sure and I don't think there is any really good theory sketching out what components of the diet that would be.

There has been research on selenium. I am pretty sure--well, actually, I am not sure about the Faroes--how is the selenium levels in the Faroes, are they fairly high? I am pretty sure they are fairly high in the Seychelles. Maybe we will that off until Philippe has his talk.

It is certainly plausible. Then, of course, you have to ask yourself would those particular nutrients be particularly high in the U.S. diet, but, yes, that is something that obviously should be considered and something that we don't have good comprehensive data on.

DR. MILLER: Dr. Fischer.

DR. FISCHER: Joe, when you chose the Boston Naming Test as the test that was most sensitive to the effects, and calculated a benchmark dose using that, why did you pick a single test instead of picking a score of a group of tests, either those tests that showed an effect or maybe even the whole neurological analysis, a score?

In other words, it seems to me what you are doing there is picking data from a single test and using it to regulate, when, in fact, you had a whole lot of data that you just seemed to not use.

DR. JACOBSON: It is traditional in risk assessment to go with the most sensitive endpoint because from my understanding, the philosophy is we want to protect, so we want to err in the direction of caution, we want to pick the most sensitive endpoint.

I was particularly comfortable with taking the Boston Naming Test because vocabulary is actually a very, very good surrogate for overall IQ, and if you had to pick a specific test that would be likely to be predictive of how the child would do later on, you would do best with the Boston Naming Test.

When we looked at the cord blood measure in the Faroe study, there was another test that was actually more sensitive, which was the Sustained Attention Test. I wasn't comfortable going with that one, first of all, because data had been collected only on half the cohort. Secondly, it doesn't have very good predictive validity to a broad range of other aspects of function, the way the vocabulary did.

I would philosophically see nothing wrong with developing a composite measure, and we considered it, but

we went in this direction to follow what is traditionally done in the field, that is, to err in the direction of caution.

DR. FISCHER: So, scientifically, you would have picked a group of scores, right?

DR. JACOBSON: Normally, but I can't make a strong scientific argument that a group of scores would have been any better than vocabulary, because vocabulary is such a robust predictor of a broad range of effects.

DR. FISCHER: Then, why do the other tests?

DR. JACOBSON: Scientists do the other tests because they want to get a comprehensive understanding of what is going on. A risk assessor may or may not take all of that information. You know, formulas are developed, procedures and approaches are developed for various reasons, and as I said, I think the rationale here is to try to get maximal protection.

DR. MILLER: Dr. Dwyer.

DR. DWYER: Are there any other confounders that come to your mind?

DR. JACOBSON: My sense was that these groups did an excellent job of controlling for confounders, and we actually looked at that in great detail in the Raleigh meeting, and were very impressed with it.

We put the Faroes people, we raked them over the coals, we made them construct an urban/rural variable, and they seemed to pass all the tests. It seemed no matter what you controlled for, the effects were still there. Sometimes the effects looked a little weaker, sometimes a little stronger, but my sense is all the things I can think of were controlled for.

DR. MILLER: Other questions?

DR. KUZMINSKI: Please correct me if I am wrong, but the question is along the same line as Dr. Fischer's, and that in your presentation here today, you have outlined the three studies and the differences and the parameters, but from what I have read in the pre-read material--again, correct me if I am wrong--the Academy committee did not consider the results of the Seychelles study in the deliberation towards recommendations to the EPA on the RfD.

Am I interpreting that correctly?

DR. JACOBSON: Well, we actually did two exercises. We did one exercise where we took the data from the three studies and integrated them. This was a statistical exercise, which is kind of averaging along the lines that Dr. Fischer was recommending, and that analysis would have led to a set of recommendations that were surprisingly similar to those that we finally did make.

But again, we felt that it was appropriate to follow some of the protocols of the way risk assessment has traditionally been done, and typically, what is done is a single study is selected, the best study is selected, the one that appears to be most valid, most sound, most solid, and then within that study, the most sensitive endpoint is selected.

So, in our final recommendations, we went with what we considered to be the traditional risk assessment approach. However, as I said, the other exercise did lead us to a surprisingly similar conclusion.

DR. MILLER: Thank you very much.

There are two speakers now dealing with the two principal studies. The first, Dr. Philippe Grandjean from Odense University to talk about the Faroe Islands study.

Dr. Grandjean.

Faroe Islands Study

DR. GRANDJEAN: Thank you. I am very pleased to be here. I have previously worked with colleagues in the U.S. EPA at the ATSDR, at the European Commission. I am very pleased to be here with FDA now to tell you about our experience in the Faroe Islands.

[Slide.]

What I am going to do today is try to look at that research and see what can we learn from that experience if we go beyond the results as such.

[Slide.]

Let me just give you a brief overview of why we chose doing research in the Faroe Islands. It is a rainy place in the North Atlantic between Iceland and Norway. It's rather cool in summer, but the winters are mild. The reason it is interesting to us environmental epidemiologists is that people in the Faroes have this tradition of eating pilot whale.

They chase pods into shallow bays, pods that come near the coast, and for hundreds and hundreds of years, the tradition has been that they kill of pods of these small whales that are nonendangered, it's a sustainable use of the species, so they get this extra supply of proteins and fatty acids, essential fatty acids and vitamins, but unfortunately, it has turned out that the meat and the blubber are contaminated with methylmercury and PCBs respectively.

[Slide.]

The reason for doing the research in the Faroes is that it is almost like a natural experiment because the pods do not come in regularly, and when they come in, when they come near the coast, you can't be sure if they will be

near one island or another island, therefore, the communities are exposed to methylmercury or PCBs on an irregular basis. You can't choose it, so it depends on availability of the whale meat.

At the same time, these people eat a lot of fish, they eat fish for dinner three times a week on the average. They eat lots of cod, halibut, salmon, the types of fish that you would normally eat when you are in the North Atlantic.

It is a homogeneous population. It is a wealthy, developed, industrialized country with scandinavian background, with what you would call socialized medicine, equal access to social support and health care. In studies we have conducted there, we have had a high participation rate.

[Slide.]

Now, this study has been in international collaboration between Faroes and Danish researchers, researchers from the U.S., Sweden, Japan primarily. So far we have looked at three cohorts, and here, I am going to talk about, first of all, Cohort 1, I will talk a little bit about Cohort 2, and we have some preliminary findings on Cohort 3.

[Slide.]

First of all, the conclusions so far from these studies have been that we see neurobehavioral adverse effects associated with developmental methylmercury exposure. We see that that exposure is also associated with increased blood pressure, poorer heart rate control, and also decreased growth of all physical growth postnatally, and we see that the prenatal exposure is much more closely associated with these adverse effects than the postnatal.

The preliminary results from the follow-up at age 14 of Cohort 1 are in agreement with the results that we saw at age 7. This is not published, so I can only give you the preliminary results.

[Slide.]

When you do research on this area, there are a couple of very crucial issues. One issue that Dr. Jacobson touched upon was the validity of the exposure estimate. If you do a regression analysis to assess the effects of an exposure with regard to some effects, your basic assumption is that the exposure is measured without error, it is a precise measure, but there is no such thing as a precise exposure measurement because what you would like to know is how much methylmercury is there at the target, let's say, of some particular part of the brain.

We will never know that, so anything else that we are using is a proxy. That means we are going to have an underestimation of the true effects of methylmercury. Now, these are the exposure biomarkers that we have used, and I will talk a little bit about those.

[Slide.]

First of all, you have to have as precise a result as possible from the layout, and I will show you briefly on the next slide what I mean when I say that. The other issue here is that the timing of the sample has to relate to the toxicokinetics of behavior of methylmercury in the body, and you also have to consider the characteristics of the specimen, and particularly that is a problem with hair.

Hair varies a lot between people, and hair structure or hair treatment even varies a lot, and that causes uncertainty. Finally, the bottom line is obviously the predictive validity, which one correlates the best with the outcomes that you are looking at.

[Slide.]

So, here are the issues in regard to the laboratory validity. I think we have done as well as we can possibly do with modern atomic absorption techniques and supporting methods. The chemists told me that the

imprecision of the microanalysis, it should be better than 5 percent.

So, being confident environmental epidemiologists, we thought, oh, wonderful, we have an exposure estimate which has an imprecision of about 5 percent, that is great, we are in a fabulous position here.

Well, I will tell you a little bit down the road that this was a naive assumption. These exposure biomarkers are not all that precise.

[Slide.]

Here is one issue, though, you have to consider, and that is a variability of exposure. Now, the colleagues in Rochester looked at hair from the Faroes that they chopped into segments, and we followed up on that issue, and we have a total of 21 long hair samples where the average was above 10 ppm that we had chopped into these segments, and these are the three that showed the greatest variability with a coefficient of variation of about 25 percent.

Actually, you can see there is only one of them where there is a definite clinal tendency. It is only 1 out of 21 samples, but anyway, this kind of temporal variability will mean that you will have an imprecision associated with just about any exposure biomarkers that you

choose, simply because there is variability during pregnancy.

Now, we have chopped this into segments of 1.5 or 1.1 cm simply because the mercury half-life is about 45 days, so each segment corresponds to a half-life. That is the reason for doing this. We have also looked at profiles with colleagues in New York, trying to see if there were shorter term variabilities.

We compared hairs from the Seychelles and the Faroes. I have reservations about the technique that they use, because the results, in my view, were not all that reliable, but the conclusion from that study was that the profiles were indistinguishable between the Faroe and the Seychelles.

[Slide.]

The first biomarker we looked at in this regard was the long hair sample of 8 or 9 cm from the women, that the hair was taken at parturition, at the time of childbirth, and this graph essentially shows you the contribution of mercury exposure during pregnancy and before actually to the hair mercury concentration in that particular sample we obtained at childbirth, which is here indicated as Week 40.

There is a lag time because some of the most recently observed methylmercury will still be in the hair

root, so it will not have made it into the maternal hair at the point where we sampled the hair, but then you can see that this type of a sample will overestimate the importance of the first and second trimesters of pregnancy.

We then, for about 600 of these kids, we were able to obtain from the remaining hair sample, if there was any hair sample or remaining after the first analysis, we were able to cut off the proximal 2 cm hair sample, the one closest to the root, and you can see from this representation that that would better reflect the end of the second and the early part of the third trimester methylmercury exposure.

[Slide.]

When we compare them as predictors of the outcomes that Dr. Jacobson also focused on, the finger tapping, the attention, the Bender/Gestalt, the Boston Naming, and the California Verbal Learning Test, you can see that there is perhaps a slight tendency that the proximal hair sample is better than the long hair sample, but these small differences are by no means significant, also because we are losing power as we get from the 900 to the 600.

[Slide.]

This slide shows you the correlation between the two hair mercury concentration measures. I have indicated

the ones with open circles where the coefficient of variation is more than 25 percent. This is about 10 percent of the samples where the coefficient of variation based on those two measurements only was large.

So those must have been the individuals where the mother had a variable methylmercury exposure during pregnancy. Now, the interesting thing is then going to be what happens if we remove the 10 percent of the kids who had a variable methylmercury exposure during pregnancy.

[Slide.]

This is what we did. We used the third exposure biomarker, namely, the cord blood measure as the independent judge. Is there any difference between stable and variable or mercury exposure, and indeed the bottom line is that if you remove the ones with variable methylmercury exposure, you get an increased power. It is easier to see the mercury exposure simply because you eliminate one source of imprecision.

So, on the other hand, this also indicates to us that variable exposure or peak exposure cannot be the reason for our seeing that there is an association with the cord blood measure.

[Slide.]

We also did a separate analysis, let's say, a neutral statistical analysis to see what are the

uncertainties involved here if we have absolutely no other assumptions other than the three exposure measures must be in some way a measure of some sort of true mercury exposure that we don't know.

Each of them has to be a reflection associated with some error indicated by the epsilon on the right of this equation. In order to solve this equation, you have to have three sets of equations, and then you can do a factor analysis.

So, we used the cord blood measure, the long hair mercury measure, and there is a third independent variable, the dietary questionnaire information, namely, how often have you eaten pilot whale for dinner during the pregnancy. So, when we fed that into the computer and calculated the overall epsilon for each of those three biomarkers, then, this is what we find.

[Slide.]

We set the loading factor for the cord blood to 1. You can see that the two other parameters are less good indicators of the true mercury exposure defined as the best, let's say, background that can be calculated from this imprecise information that we have here.

But the important thing is that the coefficient of variation is, number one, 30 percent for the cord blood mercury. This is much more than what the chemists told us,

much more than the 5 percent. The other important information is here that hair mercury is much more imprecise than the cord blood is.

This is not based on any toxicokinetic information. It is simply based on the concrete numbers for each child with regard to these three exposure variables only, nothing else.

[Slide.]

So how come a hair measure is more imprecise than a blood measure? Well, there are some issues involved here like I referred to before, that hair is not just hair, it varies between people, and there are several issues that you might want to consider, and it was actually done in the NAS report. They looked at this very carefully.

[Slide.]

I am showing you again this hair curve because I wanted to compare with the cord blood. The cord blood is, of course, obtained at the only time you can obtain it, at the time of parturition.

[Slide.]

Here, you actually have a representation of the last trimester. If we want to consider cord blood in regard to the predictive validity, you have to think of the windows of vulnerability here - is it important to have a representation of the last trimester?

People who work in developmental psychology, like Dr. Jacobson, would say the third trimester is certainly very important with regard to the programming of the brain.

[Slide.]

These are the results that we published in 1997, but what I have done here is to compute the regression coefficients as percent of the standard deviation for each outcome variable associated with a doubling of the mercury exposure.

The doubling is obviously you take the regression coefficient for the log transformation and multiply by 0.301, and then you divide by the standard deviation that is present in percent. You can do it yourself from the regression coefficients, but this way you can actually compare the results from the different domains, and you can see that it is really attention and language that appear to be the most sensitive.

Here, we are in a way going beyond the psychometric properties of each of these tests. It looks like attention and language are the modalities that are affected the most.

The important thing is here, blood is a much better risk indicator than is hair.

[Slide.]

Conclusions on these issues is that the cord blood is the best risk predictor, but it is still imprecise. We still have to consider this 30 percent imprecision, and I will get back to that. The more imprecision we have, the more we underestimate the true extent of the effect. There is nothing new in this, this is in perfect accordance with everything we have learned in the past from lead and many other situations.

[Slide.]

Now, if we go back to the regression coefficients for blood, we can actually do a sensitivity analysis and adjust for the 30 percent imprecision, and this is what I have done here. I am giving you the regression coefficients before, adjusted, and then you can see the increase.

Overall, it looks like for each doubling of the mercury exposure, you lose something that corresponds to about 10 percent of the standard deviation, perhaps a little more for attention and language, about 10 percent for these sensitive modalities.

[Slide.]

Now, I am going to talk a little bit about the outcome variables, because that is a second issue that you have to consider.

In regression analysis, you do take into account that they are imprecise, but there are psychometric issues that are important because some tests are very useful and some tests have a lot of noise involved like they may depend on the child's motivation or the testing situation or the testing situation, the training of the tester, or whatever. Many variables may play a role here, so you have to consider these tests very carefully and also the age of testing.

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These are the criteria that we use for the selection of clinical tests. Unfortunately, the Faroes is a scandinavian society, so what we did was to apply tests that are also applied in Denmark and Norway and other countries like that, also the United States, but we did use internal age standardization and we piloted the tests, we translated them, of course, and made sure that they functioned in that society before we went ahead.

[Slide.

Now, let me just point out a couple of concerns that we have about outcomes like this. The first issue I wanted to bring out is that it is important that a test has as many possible outcomes as possible meaning that if you do the clinical tests of catching a ball, it is something that pediatric neurologists do, they throw a ball in the

clinic and then the child has to catch it a distance of 10 feet, and the ball has to have a particular size. Either the child catches the ball or the child fumbles or the child doesn't catch the ball, so you have only three outcomes.

This is a very simple test, and it shows an association with mercury in the right direction, but the p-value doesn't prove anything, but if you use tests that reflect attention and which have an increased number of possible outcomes, then, the digits bend forward score is better and the computer assisted reaction time is even better than that simply because it is better to dissociate within the patterns of gray, because we are looking for some subtle, we are not looking for sick kids, we are looking for something subtle.

[Slide.

The second issue here is that some of these tests are I would say they are complicated to do the same way every time. They have to be done in an extremely standardized way, and you sometimes run into trouble if you have technicians or nurses do the test, and we have emphasized that we wanted the highest possible expertise, board-certified staff to administer the tests, and we saw a clear example when the similarities tests simply could not fit into the neuropsychologist's time allotment.

We had to move the test to another examination station where a technician did it, and when we looked at the kids that the neuropsychologist had examined, there was a mercury effect, but the result that we published in 1997 was the bottom line where we used the results from both stations and adjusted for the examiner and then you don't see a mercury effect.

The question is if it is not more reliable to look at, even if it is a smaller number, than to look at the kids that were examined by the neuropsychologist.

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Let me just say a few words about the outcomes at age 14. These results have not even been submitted for publication yet. We are still grinding confounder adjustments through the computer, but let me give you one which is reasonably simple to explain and one of the tests that Dr. Jacobson also mentioned, the reaction time measure using the NES continuous performance test.

We actually used a revised version with animal silhouettes because at age 7 we were not sure that all the kids all knew the letters--and that is a standard version for adults--equally well, but we were quite sure that they all knew animal silhouettes. So, instead of the letters, we used five different animals, and the kids had to react to the. You see this cat on the screen here.

So, the only difference between 7 and 14 years is that at 14 years, the test was extended to last for 10 minutes rather than 4, which was the time we used at 7 years. Now, this was administered by the neuropsychologist.

[Slide.

These are the results. These are the correlation coefficients that are not adjusted for confounders, but what you see here is that cord blood is still a significant predictor of the outcome 14 years later, and it is actually better than maternal hair and also better than the postnatal measures.

At age 14, it turns out that the kids' exposure at that time actually correlates pretty well with what the mother had 14 years before, possibly an indication that dietary habits are quite stable within families at particular locations.

So, when we do a multiple regression analysis, we try to leave in as many predictors of mercury exposure as possible. It turns out that the cord blood microconcentration is the only one that remains.

[Slide.

The important thing with this slide is that the beta for age is almost the same as the beta for mercury, which means that if you increase the mercury exposure by a

factor of 10, then, the child has a result which would have been similar to the situation had the child been one year younger.

In other words, if you increase the mercury exposure by 10-fold, then, the effect is similar to losing one year of development.

[Slide.

Now, let me just say a few words the Cohort 2.

DR. MILLER: Dr. Grandjean, you have five more minutes.

DR. GRANDJEAN: Okay. I will run through this quickly.

Cohort 2. These results were published in the Journal of Pediatrics. These are the results for age 2 weeks.

[Slide.

This is PCB. Dr. Jacobson talked about this. We have looked into PCB.

[Slide.

And we have validated the cord tissue PCB and even if we assume that there is a large imprecision in the PCB measure, PCB is not a significant determinant of the outcome in this study.

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These are the results from the paper published last year that shows that PCB has an effect in this population, but only in the kids who have a high mercury exposure at the same time.

[Slide.

These are results of brain stem auditory-evoked potentials from two locations, the Faroes and Madeira, and we see that the evoked potentials increase in latency, and the increase is similar in the Faroes and in Madeira.

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The results of brain stem auditory-evoked potentials used for calculation of benchmark doses are very parallel to the results that the National Academy came up with. You can see that the results for Madeira and the Faroes are quite similar to the neuropsychological benchmark doses published by the National Academy.

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These are the blood pressure results. You have the publication, so I won't dwell into that. I will just say that this is an effect which is seen below the current reference dose that the EPA has decided upon. We don't know the implications yet, but I am just saying this is an effect which is seen in very low exposure levels.

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These are unpublished data on Cohort 2 where we show the weight at age 18 months adjusted for confounders. We see that kids with the highest mercury exposure actually weigh about 1 kilogram less than kids with the lowest exposure.

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The bottom line of all of this is how do we translate this to public health. I have already said that you can compare this to the age, the effect of age on development, and the result that we see is that for every time you double the mercury exposure, the child loses some months in its development.

Ten percent of the standard deviation had this been an IQ, it would have been 1.5 points of IQ, so our results would translate to a loss of about 1.5 IQ points every time you double the exposure.

Thank you very much.

DR. MILLER: Thank you.

Questions from the committee? Dr. Dwyer.

Questions of Clarification

DR. DWYER: I was wondering if there would be any effect of alcohol on absorption of methylmercury.

DR. GRANDJEAN: The Faroes is a very traditional society where men drink, but women don't, and it is a very small percentage of women who have at all touched alcohol

during pregnancy. The Faroes have the lowest alcohol use in I think all of European countries simply because it is more traditional.

DR. RUSSELL: I wonder if you would clarify one thing for me. Is the level in codfish caught in the Faroe Islands likely to be the same as caught in Cape Cod, for example, or another geographical location?

DR. GRANDJEAN: I don't know what the level is here, but in the Faroes, the mercury content of cod is about 0.1 ppm. Does that make sense?

DR. RUSSELL: I guess what I am getting at is whether there is large geographical distribution, wide variation in mercury levels in a particular species of fish depending on the geography of where it is caught in the Atlantic or the Pacific.

DR. GRANDJEAN: I am not an expert. All I can say is that the main source of exposure is pilot whale, which overlaps with swordfish and tilefish, et cetera, but the average is higher. It is about 2 ppm. The Faroese eat it both as chunks, as steaks, and they also eat it like pemmican, like little slices, and that exposure is sort of diluted because they eat a lot of fish at the same time, so they may have some peak exposures now and then, but then they also have a background from the pemmican and the fish.

DR. LEE: I was wondering if you can give me a feel for how much the mercury in the hair comes from dietary versus environmental exposure.

DR. GRANDJEAN: What do you mean when you say environmental?

DR. LEE: Well, for example, polluted water or smoke. I mean if I am being exposed to mercury via polluted water, will it get into my hair? What kind of exposure can I expect from that?

DR. GRANDJEAN: It is possible that the hair and also the blood may contain some inorganic. In the speciation that we have done, more than 90 percent is methylmercury, and not inorganic mercury.

Methylmercury would, as far as I know, come from marine food or freshwater fish only. I am not aware of any other important sources except perhaps if there is some internal methylation of inorganic mercury, but I think it would be an extremely small contribution.

DR. LEE: So, you are saying all the mercury that I would find in my hair would be from food sources?

DR. GRANDJEAN: I would think so, but there is a possibility which has been seen in various instances that hair might absorb inorganic in particular mercury from outside sources.

DR. FISCHER: Dr. Grandjean, tell me or tell us, knowing the exposure to PCBs of this population that we have studied, would you expect that the levels of PCBs would allow a contribution of those substances to the effects that you are attributing to methylmercury?

DR. GRANDJEAN: It is a very good question and perhaps Dr. Jacobson might also contribute to this. The difference between the evidence that we have on PCB and the evidence we have on methylmercury is that the PCB studies that have been carried out in North Carolina, with the Great Lakes, and in the Netherlands, have not been adjusted for methylmercury, so we don't really know what the methylmercury contribution to the PCB associated or attributive effects might have been.

In the Faroes at least, we have measured the PCB both in Cohort 1 and Cohort 2, and we have been able to adjust for PCB, and it is very hard to see what the PCB contribution is in these cohorts because the mercury effect is so strong, so we were not able to discern any clear PCB effect.

It doesn't mean that PCB is not neurotoxic in the Faroes. It simply means that it is less neurotoxic than methylmercury at the levels that we have in that population.

DR. FISCHER: And the method you use to adjust for the PCBs, would you explain that to us?

DR. GRANDJEAN: We did regression analysis that have been published. We also have a paper in press where we used structural equation analysis, and the structural equation analysis indicates that even if we assume that our PCB measure is vastly imprecise, it never reaches a level of statistical significance of 0.05. It simply doesn't become significant, but mercury is.

DR. DWYER: Have you ever looked at meconium in the fetus?

DR. GRANDJEAN: No.

DR. MILLER: Dr. Friedman.

DR. FRIEDMAN: Is there a reason why you looked only at cognitive outcomes, cognitive/achievement outcomes, and not at social/emotional outcomes?

DR. GRANDJEAN: We looked at the Child Behavior Checklist, but we had difficulty translating it into Faroese.

DR. FRIEDMAN: What was that measure that was mentioned?

DR. JACOBSON: Child Behavior Checklist.

DR. FRIEDMAN: CGCL, okay.

DR. GRANDJEAN: Which is the standard measure, and it is only currently being standardized into the

language of Danish, and we tried to translate it and pilot it in Faroese, and the mothers simply had great difficulty answering these questions perhaps because of linguistic problems and perhaps because of cultural problems.

This is a test that has been I think developed in New Hampshire?

DR. JACOBSON: In Vermont, but it has been standardized in the Netherlands and many European countries.

DR. GRANDJEAN: Anyway, we could not apply it. We tried and we failed, and it was, in our hands, a very unreliable instrument and therefore we did not dare to go ahead with this. I think you are right, that it is an aspect that should be looked into, but I think that one should not look at that aspect in the Faroes population without having something that is standardized, and we don't.

DR. APOSHIAN: Dr. Grandjean, would you say something about the amount of selenium in the diet in the Faroe Islands, Seychelles Islands in New Zealand, please?

DR. GRANDJEAN: We measured selenium in cord blood and the average concentration is I think about 30 or 40 percent higher than in the Danish population, clearly because the Faroes depend so heavily on seafood.

We also looked at the mercury-selenium ratio as a predictor of these outcomes because both mercury and selenium were measured in cord blood, and the mercury-selenium ratio was not a better predictor than the mercury concentration as such.

So, it looks like selenium deficiency does not explain the effects, nor does high intakes of selenium protect against mercury toxicity. We have done the same exercise in Cohort 2 with essential fatty acids especially docosa-hexaenoic acid, and DHA prolongs pregnancy and mercury has no effect on birth weight.

It could be that the DHA intake protects against effects on birth weight by methylmercury, because we have been unable to see any effects. Likewise, we have not seen effects on visual-evoked potentials in the Faroes, perhaps because DHA protects the visual part of the brain.

These are research issues. I can't make any conclusions, but it is speculation that some of these essential nutrients in seafood are perhaps modifying, however, only slightly the mercury toxicity that we see.

DR. RUSSELL: I think in the Faroe Islands, the dietary fiber levels are fairly low because of a lack of a large amount of fruit and vegetables.

Is there any evidence at all that dietary fiber alters the bioavailability? It does for other metals. I have no idea about mercury.

DR. GRANDJEAN: I think the difference between methylmercury and other metals is that methylmercury is almost completely absorbed in the gut, and any interference due to dietary fibers would have a very small impact simply because of the lipophilic character of the methylmercury species. Whether it might affect the bacterial environment, so that it might affect the methylation or demethylation in the gut, I can't say, but I am not able to make any judgment. I would think, if anything, it would only have a minor effect.

DR. KUZMINSKI: Dr. Grandjean, is there, in your data, any way of backing out the effects of the whale consumption and isolating only the fish consumption, because in the comparison of the Faroese consumption of fish and whale compared to U.S. consumption, that seems to come out as the one big difference?

DR. GRANDJEAN: I think had the Faroese have exposure through drinking water, you would pose the same question. We look at methylmercury as the toxic species, and it doesn't matter from where it comes. I may be wrong, but sometimes a methylmercury concentration in the whale meat is like 0.5 or 0.8 ppm, which you would not consider

high. Sometimes it is as much as 3 ppm, and people who eat the whale meat don't know. It is only after the methylmercury has been absorbed from fish or whole or shellfish, wherever it comes from, that we can detect it, and then we measure the blood or the hair or whatever.

I would have sincere disagreements with you if you felt the methylmercury from whale meat would have any different effects from methylmercury from fish. It is the same species.

DR. KUZMINSKI: Where I was headed, this is intuitively, was trying to ascertain an effect just due to fish consumption and not whale consumption. It is not the whale mercury being different from fish mercury, no.

DR. GRANDJEAN: I don't think we can do it. I also don't think that I understand what the scientific basis would be, but even if one would do it, I don't think it is possible to do simply because people who eat a lot of whale meat also eat a lot of fish, so it is very difficult to sort out where it comes from.

DR. RUSSELL: I have one final question on the diet. Can you give us some feel for the percentage of calories coming in as fat in the Faroe Islanders? In other words, is it more or less comparative to American fat intake or is it higher because of the blubber and the lack of fruit and vegetables?

DR. GRANDJEAN: I think fat intake may be more relevant because of the lipophilic character of the methylmercury. People who would eat a lot of blubber might have a higher relative fat intake than people who eat less.

The overall average in the Faroes has not been calculated. I would assume it is similar to scandinavian levels, which are similar to U.S.

DR. McBRIDE: Do you have any information on birth weight? Fatter babies might store mercury and have an exposure after birth. Do you have any information on birth weight effects and their variables?

DR. GRANDJEAN: Number one, the Faroese have one of the highest birth weights in the world, and our interpretation is that they have such a high intake of essential fatty acids from seafood, especially DHA, and we have also been able to show that the high the DHA intake, the longer the duration of pregnancy.

I mean most of these women have a pregnancy duration of 40 weeks, some of them even 41, so it is an effect of prolonged gestation. When we tried to figure out if there is a mercury or a PCB effect, because this has been seen in some studies that these toxicants might affect birth weight, we don't see anything, but when we look at postnatal growth, we see that the prenatal mercury exposure affects the postnatal weight gain.

DR. McBRIDE: But does birth weight affect the outcome on your psychological tests?

DR. GRANDJEAN: It would have been if we had used kids who were also pre-term. All of these kids were normal full term.

DR. McBRIDE: But I am not thinking of pre-term effects, I am really thinking of birth weight.

DR. GRANDJEAN: No, birth weight does not have an effect. I mean all of these birth weights are above 2,500 grams, and we looked at it. It doesn't affect anything.

DR. McBRIDE: So, I mean you looked at birth weight compared to outcome.

DR. GRANDJEAN: Yes, birth weight was included with other risk factors like previous history of skull trauma, history of meningitis, neonatal jaundice. We looked at all these factors, and we didn't find an effect.

DR. FRIEDMAN: There is no way in your study, which is a kind of a natural history study, to disassociate the prenatal effects from later effects, right? That is, the children continued to have high consumption of the same foods that their mothers had.

Is there a way to know whether this could be reversible if the mothers had high consumption and then, after birth, it stopped, would the children look the same later on? This is all hypothetical, but I guess we are

talking a lot here about prenatal effects, and I am not sure if those are really just prenatal effects of cumulative effects over time.

DR. GRANDJEAN: There are two things here. After the child gets born, the mercury content in the child would drop way down, because the supply from the mother would cease except for those kids who get breast fed.

We see at age 12 months that there is a very clear association between the hair mercury concentration of the child and the duration of breast feeding, so those who have been breast fed for a long time have more methylmercury in the hair because the mother continues to contribute.

However, the hair mercury concentration at 12 months is only about 20 percent of the average of the hair mercury concentration of the mother, so there is less mercury coming through human milk. We can still see it, but it's less.

Now, after weaning, it is going to take some time before a child start eating whale meat. Usually, they will get other kinds of food before the mother will introduce fish or whale meat. At age 7, I don't remember the percentage of children who had started eating whale meat, but it was not a majority.

So, it is only when you get up to age 14 that they are closer to eating the adult diet. We have two issues involved here, namely, one, we have a scale of mercury, potential mercury exposures, and then we also have a scale of susceptibility that we have to take into account.

It is going to be very difficult to figure out how these two different factors play a role. The only thing we can do is to do multiple regression analysis and also structural equation analysis, and the cord blood measure is way, way, way strongest predictor of these outcomes.

DR. MILLER: One more question and then we have got to move on.

DR. APOSHIAN: Did the Faroe Island studies separate the effects of breast feeding and no breast feeding as far as the domain results were concerned? As a confounding factor, in other words.

DR. GRANDJEAN: We did two things here. We looked at milestone achievement during the first year of life, and it is very clear that there is an advantage to being breast fed that overrides the possible adverse effects of getting methylmercury from breast milk.

We have also looked at the outcomes at age 7, and there is an advantage associated with having been breast

fed for a long time. There were very few mothers who didn't breast feed at all, so I can say is there is an association with the duration of breast feeding, and the duration of breast feeding is not associated at all with the exposure level, neither mercury nor PCB, there is no association here, so it is not really a confounder, but there is a small advantage that we can see.

This is a paper which is going to be submitted very shortly, and I don't quite remember if there was a difference in the domains.

DR. APOSHIAN: Along those same lines, and this may not be a fair question, maybe I should wait for Dr. Myers, is there a difference in the length of breast feeding of a child in the Seychelles Islands versus the Faroe Islands, do you know?

DR. GRANDJEAN: All I can say is that kids in the Faroes are being breast fed much longer than kids in scandinavia. They do not live up to the World Health Organization recommendation, as nobody does, so breast feeding is the rule in the Faroes, and we see an advantage associated with it, and the duration is not associated with the exposure level.

DR. MILLER: Thank you very much.

I will take this opportunity, another member of the committee has shown up, Ms. Halloran from Consumers Union. Welcome.

The next speaker is Dr. Gary Myers of the University of Rochester to talk about the Seychelles study.

Seychelles Study

Dr. Gary Myers

DR. MYERS: Thank you very much for inviting us here to present our study.

I would like to go through the Seychelles study with you and then answer whatever questions I can.

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This is the hypothesis that we have been addressing in the Seychelles study - whether or not prenatal exposure to methylmercury from maternal fish consumption during pregnancy can adversely affect children's developmental outcomes.

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This hypothesis actually came out of work that we did in Iraq, which was mentioned earlier. This is just one of the graphs from a publication that Dr. Cox was the first author in back in 1989, and this one looks at the frequency of retarded walking, and as was mentioned earlier, the endpoints in Iraq were somewhat less sophisticated that

they were in our Seychelles study and as they have been in other studies since that time.

Retarded walking was simply defined as walking before or after 18 months of age. When one plots the abnormals versus the normals and does this hockey stick plot, if you will look at the top of the graph, there are all these little pluses, those are individual cases where the child had an abnormality of walking. Along the bottom, the pluses are all individual cases of where the child was normal in walking.

As you can see, there are a couple of things that come out of the graph. The first is that if you project this lying downward, it looks like you might have effects down around 10 to 20 parts per million. These are concentrations in maternal hair, which is, in fact, the biomarker which has been used by every other study, studying this issue, and for reasons which I will try to address briefly in a moment.

So, that is one thing. You see that down around 10 to 20 parts per million, one might expect to have some effects. The other thing that you see is that when you look at the top, there isn't any data or very little or very few points of data below about 50 parts per million.

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Following that, we actually proposed this hypothesis that these lower levels in fish might actually have some sort of adverse effect, and we looked at the literature and we came to some interesting conclusions.

First, it seemed pretty clear that the fetal brain was much more sensitive than the postnatal brain to the effects of mercury.

The second was that it looked like from the neuropathological studies and all of the other clinical things that had been done previously, and which have, in fact, been done since, that the effect really should be global. We couldn't see a reason why it would be domain specific from our review of the literature.

We decided that if there were going to be any effects from the consumption of fish at these low exposures, they would probably be subtle effects. We wouldn't expect any of the major things that were seen at Minamata.

Just an aside about Minamata, one of the interesting things about Minamata is there were either serious affected children or they were non-affected children. Nobody really described this spectrum of decreasing morbidity. Whether that was because it wasn't studied or because it didn't occur has never been clear,

but it still hasn't been described from the Japanese experience.

The other thing is that we thought that peer analysis was really an excellent way of looking at exposure and, in fact, we have subsequently looked at neuropathology in relationship to hair mercury concentrations, and they correlate better than fetal blood in our pathological specimens, and there is some evidence--and Dr. Clarkson will be down in a day or two and perhaps speak more eloquently to this--that the transport mechanism into hair for methylmercury is much more akin to what happens in mercury getting into the brain. Of course, the brain is the target organ that we are all worried about.

The last thing is that actually, you ought to be able to detect these effects early on. After all, the Iraq study, the average age of the children studied in Iraq was 30 months, so waiting five or six years didn't really make sense to us.

When Dr. Marsh talked me into going out to Seychelles and starting this study, he told me, he said if you don't find anything in six months, you probably won't find anything. It turned out that wasn't necessarily true.

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Anyway, we looked for a population that had large consumption of fish. We actually started several studies

before we ended up in Seychelles, and there were a variety of reasons why the other studies didn't work out, but it is very difficult to set up these studies. Dr. Grandjean is fortunate to have the Faroes, and we are fortunate to have the Seychelles. There are many places in the world where these sorts of detailed studies simply can't be done.

For those of you who are not familiar with the Seychelles, it is where the three red lines come together there.

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These are some of the characteristics of Seychelles, and I will be glad to elaborate on them later if anybody wants to ask, but they have a high fish consumption. Dr. Grandjean presented some evidence earlier that in Faroes, they have three fish meals a week.

Well, when I started the study there to gather the main cohort, we asked a question how many fish meals do you eat a week, and they told us 12 was the average, so between 10 and 12 fish meals a week is the average in Seychelles.

It has been a socialistic state for quite some time, for the last 30 years. They have free universal health care. The infant mortality is lower than in the U.S. They have a 98 percent immunization rate, which is better than the U.S. You wouldn't want to get sick there,

but actually, the preventive care is excellent. Free universal education. All the child start in the educational system at age 3 1/2, and it goes on from there up into the teenage years.

They have really very limited poverty. There is a social structure, but it's very compressed. There is literally no malnutrition on the island, and they quite low levels of other sorts of contaminants.

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This is downtown Victoria, which is really the only major city on the island.

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This is just the fish market. People go the market every day and buy fish or they buy it on the roadsides or the beaches, but the people eat large quantities of quite fresh fish.

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We have looked at PCBs in Seychelles, and they are really below detectable limits. We have looked at lead, and lead levels are quite low. We haven't actually measured PCBs, but we are told that the levels of pesticide exposure are substantially below the FAO Codex Alimentarius reference levels for a problem.

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So, as best we can tell, the other sorts of exposures that one might be exposed to are very low levels.

Let's go back to that slide a second.

We measured prenatal exposure in maternal hair. This gives you really a very excellent index of exposure for the whole pregnancy as opposed to just the final trimester. We have not measured cord blood in Seychelles. The exposure averaged about 7 parts per million and ranged from below 1 part per million up to about 27 parts per million.

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This gives you some idea. We adopted a longitudinal design to the study which I will show you in a moment, but this gives you some idea of the numbers of children that have been seen at each one of these ages, so we have actually examined these children on five occasions now.

We have been able to maintain quite a substantial number of the cohort. It is a small island, there is not a great deal of the population that emigrates, and it is easy to find them.

We have excluded individuals for various reasons. Among the 39, the major reason for exclusion was that we really couldn't recapitulate their mercury exposure. When we looked at the hair samples that we had, we simply

couldn't recapitulate their exposure, but we have also removed from the cohort, a few individuals who had perinatal seizures, intraventricular hemorrhage, substantial head trauma, and other things that are known to be highly correlated with abnormal children's development.

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We looked at a variety of covariates in our population. We have looked at socioeconomic status, IQ. We have been to every one of the homes in Seychelles and assessed their home environment with the Caldwell Bradley assessment of the home.

We have looked at maternal smoking and alcohol. They are extremely low in Seychelles. We have looked at the medical history of the mothers, and we have also looked carefully at the language spoken in the home. About 98 percent of the people there speak Creole, so the vast majority of them actually have Creole.

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This is simply one of our testing rooms and one of our testers administering the KBIT for maternal intelligence.

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This is a typical home in Seychelles. The two women on the left are the nurses who were in the home doing the home environment, the HOME Scale.

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We have looked at a number of covariates that affect the children. We have looked at gender obviously, because that is a significant thing. We have looked at hearing in the children. We have looked at their health history, their birth weight, gestational age, birth order, length of breast feeding, and a variety of other things.

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This is the design of the study. We started the main cohort. We did have a pilot cohort, as Dr. Jacobson mentioned earlier. The pilot cohort was done originally by myself before we started the main cohort, and then I went to Seychelles and lived there for a year to enroll the children at the six-month evaluation, so I did all of the Denvers and Fagans and neurological examinations at that point in time.

Subsequently, we have used a battery of Seychelles professionals who have done the testing for us. We have now examined the children, over 700 children at each one of these five points, and the list of test is shown there.

I did put down in the corner there, there has been a double-blind study just to remind myself to mention to you that from the beginning, we have never shared mercury levels with anyone in Seychelles, nor with any of

the investigators who are clinically looking at the data. So, it has been double-blind from day one, which goes back to about 1987. The Seychelles have been very cooperative with that.

They have reviewed all of the data that we have published and made their own decisions about their choices in terms of regulation.

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We have felt that the most important thing is not so much the tester, although we have used professionals, but doing reliability on the testers to be sure that, in fact, they are reliable. So, we have used two types of reliability.

First, we have used what we call the gold standard. The gold standard is one of our psychologists from Rochester, a Ph.D. psychologist, who goes to Seychelles, sits down with the tester, and actually scores the test while the tester is administering the test.

Then, we have used interscore reliability, which is each week we have two of our testers score the same child independently, and we have compared them. We have looked carefully at those statistics, and they have had very high correlation.

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This is Dr. Davidson here on the right, one of our nurses, is simply doing a gold standard.

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When we looked at our results during infancy, this is what we found. We did find the expected effects of covariates - maternal intelligence, birth weight, and other things. We had most r-squareds for our study. This is consistent with what has been found in most developmental studies.

We did not find any adverse associations between the prenatal exposure and any of our endpoints at 6, 19, and 29 months. We did one association between an item from the infant behavior record and methylmercury, and at 29 months, on the infant behavior record, there was a decrease in the examiner's scoring of the activity level, and it was present only in boys.

We have been confused as to how to interpret that. It is a very subjective endpoint, the infant behavior record, and we are not sure whether it is better for boys to be less active or more active.

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We like data. We like to see the points and share them with people, and let them know what, in fact, the data looks like. This is the visual recognition memory on the top and the visual attention on the bottom. This is

data from the Fagan test, which is I am told by psychologists felt to be one of the premier tests for intelligence at these early ages.

This is at the 6-month examination, and there was no association with mercury within the range we have been studying.

[Slide.

This is data from the 29-month examination. This is the metal developmental index from the Bailey, at 19 months on the top and at 29 months on the bottom, and that is on the left. On the right is this infant behavior record. You can see that in girls, the slope is flat, and in boys, it tails off as one goes to higher mercury levels. That is the association that we are not sure whether it is a beneficial or adverse association.

[Slide.

When we get up into early childhood, again, we find the effects that we would expect from a variety of different covariates. Again, most r-squareds. Again, no association between exposure and the endpoint. We did find one beneficial association

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This is the McCarthy GCI adjusted for covariates, and these are partial residual plots. Again, we like data. This is the 66th month examination all plotted against

prenatal methylmercury exposure, and there is no significance there.

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This is the PLS language score adjusted for covariates at 66 months. There is an association, but it seems to be a positive association here, we are not sure what to make of that, but no adverse association.

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This is the Woodcock-Johnson applied problems, which is the mathematical part of it. Again, no association at 66 months.

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This is the Bender. What you see here is that this is the errors on the Bender test. What you see is that males are flat and in females, there is a slight downward slope meaning fewer errors. This is one of the ones where when it goes down, there are fewer errors, so that is a beneficial effect.

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At 107 months, we examined the children again. This is the nine year evaluation, which we are in the process of publishing. Again, we looked at socioeconomic status, maternal IQ, age, family status, health history, and the home environment.

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For the child, we did use postnatal methylmercury, age of testing, gender, hearing level, and examiner. We have included examiner in these analyses, as well.

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This is just one of the tests. I just have a couple pictures of the tests. This is finger tapping. It is how many taps you do in a certain period of time.

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This is a grooved pegboard using either preferred or non-preferred, and these are little pegs that have a little notch in them, and you have to fit them into holes. It is how quickly one can do the test.

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This is a picture completion. It is just a series of pictures, and you have to put them together in a story from the WISC.

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This is from the Woodcock-Johnson test.

DR. MILLER: Dr. Myers, you have five more minutes.

DR. MYERS: Okay.

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When we looked at the results from the 107th month evaluation, again, we found the expected associations

with covariates. Again, modest R-squareds. Out of the 21 endpoints that we examined, we found 1 adverse association and 1 beneficial association.

[Slide.

This is the Connors Teacher Rating Scale, the hyperactivity index from it. We had every teacher of all of our main cohort children evaluate the children on this scale, and the line goes down, which is a beneficial effect.

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This is our adverse effect here. This is the grooved pegboard, and it is of the children using their non-preferred hand, and what you see is that in females, the slope is essentially negative, it is not significant, or flat and nonsignificant.

In males, one sees that there is a slight upward slope here, and that means that it takes them longer to do the grooved pegboard, so that would be an adverse effect.

So, out of 21 endpoints, there is 1 adverse effect we found at 9 years of age.

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This is just a graph to show you the effect of covariates on the various tests here. We found a lot of associations with covariates, so we have every confidence

that the tests are working there. They are picking up other things that we know affect child development.

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So, our outcome so far is that we found a lot of associations between predictors and between covariates of the endpoints at every age. We have not found an association with mercury exposure from the fish consumption.

I didn't mention, but the people in Seychelles do not eat whales at all, they don't eat sea mammals, it is purely fish consumption. All of these associations were in the direction that one expects. We have only found one adverse association in our five evaluations.

That raises the question of how do you interpret it. Well, it is good to remember that we were the group that originally raised the issue from Iraq and proposed the hypothesis, so we like to think that, you know, our studies have become more sophisticated since that time rather than that we have lost our ability scientifically.

So, we look at other interpretations. One interpretation may be that the exposure level is simply below the toxic threshold. Another possibility, though, that we are currently exploring in Seychelles is that there is neurotoxicity, but somehow it is modified at these levels. Either there is something beneficial about fish

that overcomes whatever the toxic effect is, or maybe there is something else in fish that is mitigating that, either fatty acids or selenium or something else.

We are looking currently at a new cohort that is being studied very carefully from the time the women are first pregnant, looking at these nutritional factors. The other possibility is that perhaps there is toxicity, but it simply doesn't occur until much later in life.

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We like to think that the Seychelles is a bit of a sentinel population for the U.S. One reason is that the source of exposure is about the same as what we have here in the U.S. It is really open ocean fish.

The second reason is that we have looked carefully at the mercury content of the fish in Seychelles, and it is very similar to what is on the market here in the U.S., but, in fact, the women's hair levels are between 10 and 20 times those of the U.S. levels.

So, we like to think that perhaps Seychelles could serve as a sentinel population for the U.S.

I would be happy to answer questions.

DR. MILLER: Thank you.

Comments, questions from the committee? Dr. Friedman.

DR. FRIEDMAN: Dr. Myers, I was wondering whether--I am sure you looked, but only didn't present--at interactions. Do children of poor quality home environments show different outcomes relative to the effects of--

DR. MYERS: We have included socioeconomic status in all of our analyses.

DR. FRIEDMAN: You controlled for everything.

DR. MYERS: Yes.

DR. FRIEDMAN: But I am asking whether if you took out the control of the HOME, for example, and then looked at the children who are high on the HOME versus low on the HOME, would you find the same relationship holding in the two extreme groups.

DR. MYERS: We have looked at social effects, and there are some. I am not very good at this. Dr. Cox, who is in the audience, may recall the social effects better than I.

Chris, the question has to do with the social effects on the outcomes.

DR. FRIEDMAN: The interaction.

DR. COX: I will do my best. As I heard it, the term was interaction, so the way I would interpret that is to ask whether the effects of mercury are modified by

levels of other variables, for example, socioeconomic status.

Is that the question?

DR. FRIEDMAN: I guess so. Let me try to phrase it. I realize there are many things that operate to produce the outcomes that we see on psychological testing, and what we are trying to do with statistical analysis is to clean out the effects of variables that we are not interested in and ask if this was an experimental design, would mercury have an effect, but as I said before, we realize different things work together, and it may be that a high-quality family environment and high-quality out of home environment actually work against the ill effects of mercury.

DR. COX: That is modify the effect.

DR. FRIEDMAN: Right.

DR. COX: So, we are both saying the same thing. Do levels of whatever factor you might want to look at change or modify the association between mercury and outcome, right?

That is I think what is usually meant by the term "interaction." Because of results in a study done in Canada, we felt there was some evidence for an interaction between gender and mercury, and that interaction was

included in all the models that we looked at, and you saw an example of that here.

Dr. Davidson, who unfortunately couldn't be here today, was also interested in interactions between mercury and other variables - socioeconomic factors, maternal age, what have you. One problem was looking at such interactions, there is a very long list, and one can look at a great many interactions, and it is difficult. You have to be careful, we all have to keep our hats on.

I am a statistician, I am not a toxicologist, I am not a developmental psychologist, but my sense is that it is difficult to know what interactions one ought to look at.

We have, however, done, to get to the answer to your question, we have done and published some analyses looking at interaction effects. I can give you a reference to a paper if you are interested.

I didn't know that that question would come up, so I can't summarize the results very well for you, but my own view is we didn't find anything that was very consistent, but we did find some evidence for differential effects. It is hard for me to know what it means.

I think that kind of question is very difficult. There has been some work done in the lead literature, as well, looking for interaction effects. It is tough. So, I

don't think, besides gender, I don't think we have any very consistent evidence for modification of mercury effects by other variables that would be from the Seychelles study.

DR. FRIEDMAN: Thank you.

DR. MILLER: Dr. Nordgren.

DR. NORDGREN: This may be unrelated, but a recent area of controversy is the subject of autism, and I was going to ask also Dr. Grandjean, did you find any increased level of autism on the Seychelles or in your cohorts?

DR. MYERS: Well, the answer is no, but I qualify it by saying we have not done tests for autism. In fact, we are in the process now of putting together a proposal to do that very study with detailed tests looking for autism in Seychelles to see if there is an increased incidence.

Just from our casual experience, we have not recognized it, if there is, but that doesn't mean that it is not there.

MS. HALLORAN: Do you have information on the types of fish that were commonly eaten and what the mercury levels were, the range commonly seen in those species, and whether there is any season variation? I am trying to get at whether there might have been peak exposures or it's a very constant exposure.

DR. MYERS: We have looked at hair analyses longitudinally, and there are season variations, but they are not like what we saw in Iraq. They are down in the low range, and if they go up 30 percent, they go from 6 to 7 or 8 or 9, so it is within a very narrow range basically even though there are seasonal differences that we have seen.

We have quite a bit of information about the mercury content of fish in Seychelles. The majority of the fish eaten, probably the commonest species is the species called Karong, and the mercury concentrations in it are below a half part per million, down around 0.3.

They eat a lot of reef fish, and the reef fish, some of those are some of the lowest concentrations that we have ever recorded in fish.

DR. MILLER: Can we let Dr. Dwyer ask a question?

DR. DWYER: Thank you. Just two perhaps silly ones. One is do you have any information on fetal wastage, and secondly, were there other prespecified interactions that you looked at.

DR. MYERS: As far as fetal wastage, we don't really have any information on fetal wastage, so I can't really provide anything on that. We have thought about looking at it, but we have not done it yet.

As far as other interactions, the only interaction that we have consistently had in our analyses

is that for gender. I think that is correct, isn't it, Chris?

DR. COX: Yes.

DR. APOSHIAN: Dr. Myers, as I remember from the Raleigh White House Conference and from the NIEHS, the recommendation was made that both groups standardize the neurobehavior tests or neuropsychological tests being used.

The 107-month study that you say is in press or is about to be written, either one, does that have the same tests that were done in the Faroe Islands? I wasn't quite certain about your abbreviations. For example, the Boston Naming Test, was that done?

DR. MYERS: Actually, the tests are almost identical. The Faroes were good enough to share their test battery with us, and we looked at the tests and decided what to do, and there is a great deal of overlap in the testing.

DR. APOSHIAN: The second question I wanted to ask was everyone, of course, is concerned about the difference between the Faroe Islands and Seychelles Islands. Nowhere have I seen anything take into consideration racial, genetic makeups. For example, for N-acetyltransferase, as I am certain you know, but let me just say for the others, that the American population is

quite different from the Chinese mainland population, which is also different from the Egyptian population.

Has any attempt been made to do genetic markings or genetic marker tests to see whether the differences between the Faroe Islands and the Seychelles Islands studies on methylmercury are due to difference in genetic makeup?

DR. MYERS: I don't know whether that has been done in the Faroes. We have not done it in Seychelles. As part of our current study, studying the nutritional components, we are measuring some DNA things, but not a wide range of them.

I think there are a lot of differences between the Faroes and the Seychelles. One is in cold water, one is in warm water, one is predominantly scandinavian, one is predominantly African in origin. Their diets are vastly different really. The exposure is different. There are a whole series of things that differentiate the two populations in my mind.

DR. MILLER: Dr. Lee.

DR. LEE: Dr. Myers, your last slide indicated that we are eating some of the same seafoods here in the United States, yet, the maternal hair there is about 10 to 20 times the mercury than U.S. samples.

Do you attribute all of that 10- to 20-fold difference to diet?

DR. MYERS: As far as we can tell, it is dietary, yes. They literally eat fish twice a day in Seychelles. Even given a choice, they love fish.

DR. LEE: So, that is corroborated by your direct measurements of the mercury in the diet?

DR. MYERS: No, that is not corroborated by mercury measurements in the diet. We are currently doing that in a new cohort. The main cohort that I have just been talking about, this was examined longitudinally five times over nine years. That cohort was enrolled at six months of age, so we did not do things prospectively in that cohort.

We had prenatal exposure because we had been collecting hair at antenatal clinics for a long time, so we had quite a bit of prenatal exposure data on all of these women, but we didn't have other things. We didn't measure nutritional factors during pregnancy, which we are doing with this cohort.

DR. MILLER: Dr. Fischer.

DR. FISCHER: Looking for differences between the two studies, have you looked at the differences in preparation of the fish in each case? I have no idea how

the whale meat is eaten, for example. Anyway, the possibility exists that there could be something there.

DR. MYERS: My only experience with whale was when I attended a conference there, and they eat it, like Dr. Grandjean said, as pemmican, you know, just a chunk of blubber and you put it in your mouth, and I think it is an acquired taste myself.

[Laughter.]

DR. MYERS: As far as food preparation in Seychelles, you know, they are eating fish twice a day, they are eating a great variety of fish, and really it is prepared in multiple different ways, and we are actually looking at preparation and other things for fish at the current time, but in the main cohort, we did not do that.

DR. MILLER: Just the one question. Hopefully, as the Chair, maybe I could ask the last question before getting on.

Why don't you ask your question and then I will hopefully get to my naive one.

DR. ACHOLONU: The last speaker, Dr. Grandjean, made reference to the fact that the concentration of methylmercury drops after a child is born, and you have said that the toxicity of methylmercury may show later in life.

What I would like to know is, is the concentration cumulative in the person, the concentration of methylmercury, is it cumulative in the person?

DR. MYERS: Well, there is a half-life to it, and there is excretion, but it is slow excretion. We, as in the Faroes, have measured hair levels in the children, and they are generally fairly low until the children get older.

It is excreted some in breast milk. Chris, do you want to answer that?

DR. COX: Well, I think Dr. Clarkson will be here, you could ask him, but I believe the half-time is 50 days.

DR. MYERS: That was mentioned earlier, that is correct, 45 to 50 days.

DR. MILLER: Just one question that kind of puzzles me. Given actually in both populations, but given in the Seychelles that you have a population that is compressed socially, I think you said, that this is a relatively isolated community, at least in terms of its dietary sources, what explains the 27 times variation that you found I think in your hair?

DR. MYERS: That's a good question. I am not sure we have an answer. We have assumed that it is dietary and related to the species of fish that is being eaten and favorite. People have different favorites, and there are

fish that have higher concentrations. Mackerel and bekin, which is--I have forgotten the name--barracuda, barracuda, shark do have higher concentrations.

So, if you eat enough of the higher concentration fish, that could explain everything, but we have not studied it specifically.

DR. MILLER: Thank you very much.

We are going to call a break now, 10 minutes, please, and be back about 10:15.

[Break.]

DR. MILLER: The next speaker is Dr. Christopher DeRosa from Centers for Disease Control to talk about the recommendations from the Agency for Toxic Substances and Disease Registry.

Agency for Toxic Substances and Disease Registry

Dr. Christopher DeRosa

DR. DeROSA: I would like to thank FDA for the opportunity to share with you some of our Agency's perspectives regarding the Agency's views on mercury and related compounds. I would also like to acknowledge my colleagues John Risher and Dennis Jones, who assisted me in preparing some of the materials for today's meeting.

Today, what I would like to do is provide you a brief background of our agency. We are affiliated with the Centers for Disease Control, but we are actually one of

eight independent agencies of the U.S. Public Health Service within the Department of Health and Human Services, and we are the primary health agency or the primary federal agency dealing with the implementation of the health mandates of Superfund.

It is not totally incorrect to affiliate me with CDC because our administrator is also the director of CDC, as was currently announced, Dr. Julie Gerberding.

I would also like to provide a chronology of some of our key activities over the years, talk about the rationale for the position we took in our toxicological profile, a document that we published in 1999, an update of two previous toxicological profiles, and then some insight as to our future activities and some current ongoing activities that may have a bearing as this dialogue at this meeting will have as we go forward with a reassessment of methylmercury, as well as other forms of mercury.

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Among the health mandates that we have under the Superfund or CERCLA legislation are to prepare toxicological profiles. These are documents that appear and publicly reviewed, articulating what we know in the broad areas of exposure, toxicity, and epidemiology.

They attempt to provide health guidance for methylmercury, as well as other compounds that identify

what the adverse effects are that we need to be concerned about and at what level those effects might be a concern.

These are based on a list of priority pollutants that we prepare in conjunction with our colleagues at EPA on a biannual basis. It lists in priority order the 275 substances most frequently encountered at waste sites, on controlled hazardous waste sites, based on the probability of human exposure, toxicity, and frequency of occurrence at those sites.

So, we have prepared 250 profiles addressing some 1,000 chemicals, and they are inclusive of mercury, which is No. 3 on our priority list of 275 chemicals.

We also are mandated to initiate a research program, an applied research program to address what we don't know. I think it is important that the profiles, in addition to setting forth what we do know, also address what we don't know, which is sometimes a challenging effort in terms of identifying mechanisms to fill those data gaps, but we have identified 200 priority data needs, and they are currently addressing those in cooperation with our colleagues at EPA, NIEHS, and through some grants mechanisms, as well.

Once a site becomes listed on what is referred to by EPA as an NPL or National Priorities List site, we are

required by law to prepare a public health assessment on the health hazards associated with that site.

This is based on four general avenues of information - health outcome data that the community might provide, what the community concerns are, environmental monitoring data provided by EPA, as well as the information contained in our toxicological profiles prepared on those substances that might be encountered at a given site.

Finally, we are required to update those profiles at intervals not to exceed three years. Our first profile on mercury was released in 1989, and we have had subsequent updates on two occasions since then.

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This slide is really some of what we knew and when we knew it in terms of the documentation regarding mercury. I mentioned the first profile in 1989. In 1993, we updated that profile using the Iraqi study to develop the chronic MRL of 1 microgram per kilogram per day, similar to EPA's current value.

We had convened an expert panel to discuss a benchmark dose approach for methylmercury, but we are advised that the Iraqi study at that time had been somewhat overextended and overinterpreted and that it would be better that we wait for the outcome of the information coming out of the Seychelles.

We convened a second expert panel in '95 to address the issue of bioavailability. This is working intermittently, which is worse than not at all, and then we began consideration of the update of our profile from '93 based on the publication in 1995 of some of the data coming out of the Seychelles.

So, we initiated the update in '97, and the next slide is a continuation of that.

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We involved in that process an extensive peer review process including an expert panel review of the post-public comments that we had on the draft that was released for public comment. We had representatives of EPA and other federal agencies, but importantly, from the Faroes and the Seychelles there to further vet some of the data that they had developed to date.

I am sure there is an activation point on this one, too, but I can't quite see it, but at any rate, the point being that one of the things that we were strongly reliant on was this workshop that was referenced. It was a workshop initiated by the President's Office of Science and Technology Policy.

It was one which brought together four expert panels in some broad disciplinary areas to really dig into the critical data sets, not only in the Seychelles and

Faroes, but some of the work that Donna Mergler [ph] in Canada had done, as well as others.

So, we followed that very closely and we used that as a key basis for some of the decisions we made in releasing the mercury profile to the public. I would like to just mention for a second that our mandate is one of getting information in the hands of citizens, so that they can make informed decisions about their health.

In addition to methylmercury, elemental mercury is an issue from the standpoint of emergency response, which we also have responsibility for under the National Contingency Plan. It is the number one agent that is involved in emergency responses at our agency.

We also have concerns about the salts of mercury, also dimethylmercury, which was responsible for the unfortunate death of a researcher at Dartmouth because it is used as a calibrating agent in some instrumentation.

More recently, since the publication of the profile, the question of the safety of vaccines has come into play based on the use of thimerosol ethylmercury as a preservative in batch vaccines, and then finally, more recently, we have become very concerned about the use and misuse of chelation therapy by a number of individuals who are profiting at the expense of both physiologically and

financially of the people they are treating in some instances.

The next slide really talks a little bit about what you have already heard, and I am not going to spend a lot of time on this because it has already been discussed at length.

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I would say that two key issues with respect to the Seychelles that have been cited is this issue of lack of an effect although we now have seen that there are effects. The reason that lack of an effect may be of concern to some is that it may suggest that your protocol was not vigorous enough to detect what you were looking for, there may be some other issue that you need to be concerned about, but they have, in fact, demonstrated some enhanced performance on some of the tests and, as we just saw, one report of an adverse effect in addition to the one at 29 months in the boys.

Then, the missing domain-specific endpoints that had not yet been assessed at 66 months was something that we took into consideration in our treatment of uncertainty, and we relied in part on the Faroes data to help us deal with that.

In terms of the Faroe Island, another excellent study, we have the benefit of two very fine epidemiologic

studies. There is the issue of the type of and duration of exposure. By that, I mean the whale blubber being consumed perhaps once to twice a month at relatively high levels, 3 parts per million as opposed to 0.3 parts per million, which is characteristic of fish sold commercially in this country.

Then, the concurrent exposure to PCBs and other persistent organic pollutants. PCBs are at levels 10 times higher than in the U.S. population in the Faroes, and at three times the level of FDA's tolerable daily intake.

Other persistent organic pollutants are also a concern because PCBs are generally considered to be a marker for other POPs. For example, DDT is present at a level, in terms of exposure, five times our health guidance value for that compound.

This has already been referenced in terms of the work of Todd Kelstrom [ph] and his colleagues done in New Zealand, and the sensitivity to outliers. The initial report, the initial analysis was not significant until one of the most highly exposed individuals, who showed no adverse effects or associations, was deleted, and then we did see the association in some areas become positive. So, that is just the issue of the sensitivity to one outlier, and the question is, is the outlier relevant statistically, is it relevant biologically, and I think as geneticist

Dijanski [ph] said many years ago, "Treasure your outliers or your exceptions." That is a significant issue.

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Now, going ahead to the workshop held in '98 in North Carolina, you can see a very distinguished panel dealing with the confounders and variables issue including Dr. Jacobson, who is here with us today.

I would like to share with you just some of the findings that we have really centered on as we went forward in trying to bring our document to closure, because I think it illustrates some of the deliberative process and some of the key concerns that we had as we attempted to deal with this issue.

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This is the first of one of the findings dealing with PCBs. When PCBs and mercury are included together in the model that was used to analyze the outcomes, one of the outcomes is specifically related to mercury exposure, one of the four that had been reported as positive. For the other three, which included the Boston Naming Test, both PCB and mercury effects fall show of conventional levels of statistical significance. So, I think that that is a key finding that we focused on.

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Again dealing with this issue of PCBs is that it is likely that both of these contaminants adversely affect these three outcomes, but the relative contributions cannot be determined given their co-occurrence in the population.

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Finally, regarding the concurrent PCB exposure, the Statistics and Design Expert Panel determined that the best method to deal with this would be to study a population where exposure to PCBs is not an issue.

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This is simply a listing of those individuals who served on that, and these people have published extensively in this field and are recognized obviously as experts in the field.

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Turning now to a little bit about the health guidance value, well, let me just back up and talk about why we use the Seychelles cohort as the primary study, but we also relied heavily on the Faroes study, as well.

With the exception of two things, these issues, these attributes are all linked to both the Faroes study, as well as the Seychelles study. The two that I would like to bring out, that I think relate specifically to the Seychelles, is the issue of the pattern of exposure and the levels of exposure over time.

Obviously, there are 10 to 20 times higher levels in the Seychelles, but it is not because the fish is more contaminated, it is because they eat more fish. They have the highest per capita consumption of fish in the world.

Then, the issue of confounding factors, we felt that there were fewer personal and lifestyle confounding factors, that it is a relatively pristine environment, and those levels of some of the other contaminants of concern were shared by Dr. Myers. As he also pointed out, there is basic health and education infrastructure that is really quite remarkable in my mind, having had the opportunity to visit and observe some of the activities of the researchers there, and then again this issue of confounding for a number of other factors.

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Turning to the issue of health guidance, there are a number of different terms used for health guidance factors. They are very much analogous in the way that these different terms are derived. Our agency uses the term "minimal risk level," which is analogous to the reference dose, the tolerable daily intake, and previously referred to as the "acceptable daily intake."

So, it is an estimate of exposure that is thought to be without significant risk of an adverse health outcome

over a given route and duration of exposure in addition to deriving chronic oral exposures, chronic inhalation exposure guidance values, we also deal with acute, defined as less than 14 days, and intermediate, 15 days to a year in our documents.

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This is the generic formula that we used to derive a minimal risk level. If it is not visible, it is probably because there is a rule that you have to have at least one slide that no one can see when you present. This probably is not the only one, but at any rate, the MRL is simply derived operationally in a very straightforward way, analogous to the reference dose.

You identify a toxicity benchmark, a no observed adverse effect level, or a low observed adverse effect level, or a benchmark dose, as was mentioned earlier, divided by an uncertainty factor whose magnitude is inversely related to our confidence in the database. The larger the uncertainty factor, the less our confidence in the database.

DR. MILLER: Dr. DeRosa, you have 5 minutes more.

DR. DeROSA: Thanks.

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In the derivation of the MRL, the issue is that you have mercury ingested by the mothers, the offspring of

the group of concern. Hair mercury levels are measured in the mothers, and you have to have hair-to-blood ratio in order to calculate a daily intake based on the blood concentration.

Fortunately, we have some very good human data to provide this ratio. The point of central tendencies of about 14 studies is about 250 to 1.

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This just shows you some of the calculus that goes into identifying what the dietary intake is. It is related to this issue of the fraction of the daily intake that is actually taken up by the blood, which is defined by what is absorbed, and then what portion of what is absorbed actually makes its way into the bloodstream. It also is related to the blood volume, which is about 7 percent. That is about standard, about the second trimester of pregnancy.

This is what we have the concentration in the blood is based on what we see in the hair and the ratio that I just mentioned.

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This just lays out the mathematics of this and the concentration in the blood that equates to dietary intake in milligrams per kilogram per day was divided by an

uncertainty factor of 4.5, providing us with an MRL of 3 micrograms or 0.003 milligram per kilogram per day.

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Some people say that I posed for this, but I did not pose for this slide. How certain are we about what we know?

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This attempts to lay out--this may be one of those other illegible slides--the standard factors of 10 that are typically used in deriving an MRL, 1 to 10 for human variability, 1 to 10 for animal to human extrapolation, 1 to 10 for extrapolation from an NOAEL to a LOAEL, a modifying factor to adjust for scientific quality of the database lack missing datasets perhaps, and 1 to extrapolate across duration.

Some have said that we do this because we have 10 fingers, but these are biologically distributed phenomena that we are looking at, generally speaking, so dividing by 10, you encompass 95 percent of the variability. So, it does have some basis in biological science.

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This slide simply sorts out our treatment of uncertainty. Because we have human subjects being assessed, there is no species-to-species extrapolation factor other than 1, because we used the NOAEL identified

in the Seychelles study. We used a 1 because of the issue of lifetime or long-term study over multiple generations or exposure over multiple generations we use 1.

In terms of human variability, we used a factor of 3. This is a factor of 1.5 for pharmacokinetics, which we had determined through some modeling that I believe Harvey Clewell or Kenny Krump [ph] did for us, and then we have the World Health Organization Steering Committee on Risk Assessment pointed out, and I participated as a member of the Steering Committee, that these are equally determined by pharmacodynamics and pharmacokinetics. Kinetics is how it gets there, dynamics is what does it do once it gets to the target.

So, we added these two components of this, and it sometimes has been said that we multiplied uncertainty factors. We did not do that. We added these two components of this uncertainty factor and then multiplied it by a modifying factor of 1.5 to account for our concern regarding domain-specific effects out of the Seychelles.

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In summary, we have MRLs for multiple forms of mercury. The critical study was based upon some of the things that I have just mentioned and that have been touched upon elsewhere.

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Some ongoing activities. We are just again following the science, where it leads in terms of the data coming out of the Seychelles and the Faroes. We have developed an interaction profile on the contaminants typically found in contaminated fish in this country in cooperation with EPA's Office of Research and Development.

We are engaged in a study in the Czech and Slovak Republics to look at perinatal exposures to persistent organic pollutants. We are looking at thimerosol in some rodent studies to identify the comparative kinetics of thimerosol and methylmercury , and it turns out that while methylmercury has a half-life of from 45 to 50 days, thimerosol ethylmercury has a half-life about one-fifth of that.

We are planning a chelation workshop to come around this issue of chelation. The mercury document also served as the basis for WHO's International Assessment document recently released. John Risher, who is here today, is the author of that document. We are participating in the OSTP-CNR Working group.

I think there is one more slide and I will be finished here.

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Obviously, there is a lot of work going on, not only on methylmercury, but other forms of mercury. We are

committed to a continuing evaluation and understanding insofar as we can reduce uncertainty and provide some improved guidance to the public.

We will be looking carefully at the deliberations of bodies, such as this, as we go forward with the update of our tox profile later this year.

Thank you.

DR. MILLER: Thank you.

Questions, comments?

Questions of Clarification

DR. HOTCHKISS: I just wanted to make sure that I understood. You went through your MRL pretty quickly. Your kind of bottom line number was 0.3 mcg/kg/day?

DR. DeROSA: It was 0.3 mcg/kg/day, and it was 0.0003 mg/kg/day.

DR. HOTCHKISS: Then, I got that number, and that is based on a number of factors, but, in essence, on one or more studies during the outcome of exposure during pregnancy, is that correct?

DR. DeROSA: Yes, the two studies that were pivotal there were the Seychelles, we used the mean hair level and the highest quartile studied in the Seychelles of I think it was 15.3 ppm in maternal hair, converted that to a blood level, then used that blood level to back-calculate

a daily intake, and that daily intake was then divided by the uncertainty factor of 4.5.

DR. HOTCHKISS: And the 0.3 mcg/kg/day, can you tell me when your agency publicly released that amount and what the response to that has been? Is it published in the scientific literature?

DR. DeROSA: The 0.3?

DR. HOTCHKISS: Yes, and the rationale for it.

DR. DeROSA: Yes, the rationale and the overall evaluation of the database is in the toxicological profile on mercury. That is about a 750-page document. It went through some extensive peer review, as well as public comment period.

We have had a range of different comments on that. There is a wide spectrum of opinion about what the health guidance value for mercury should be, but I think that more important than what the divergence of what that opinion is, is that there is no disagreement that methylmercury is a neurotoxicant of the first degree, the one that we have to be concerned about minimizing exposures to, and that while we continue to espouse the benefit of fish as a component of the diet, that because mercury is bad, if you had consumed fish with highly contaminated levels of mercury, there may be implications for your health depending on the time of your exposure.

DR. HOTCHKISS: Thank you.

DR. MILLER: Dr. Nordgren.

DR. NORDGREN: I was wondering, would it be possible for you to make copies of the last few slides on how you determined this?

DR. DeROSA: Yes, we can make those available to you.

DR. NORDGREN: I think that is kind of crucial to what we are trying to do here.

DR. DeROSA: Right.

DR. MILLER: Other questions or comments?

If not, we thank you very much. It looks like we are right on schedule.

We will now break for lunch. Please be back here at 1 o'clock. We will begin at 1 o'clock precisely whether it's just me or anybody else.

[Whereupon, at 11:50 a.m., the proceedings were recessed, to be resumed at 1:00 p.m.]

AFTERNOON PROCEEDINGS

[1:00 p.m.]

DR. MILLER: I call the committee to order.

Our first speaker this afternoon is Dr. Penny Kris-Etherton of Penn State University, who will be talking about consumer messages.

Dr. Kris-Etherton.

Consumer Messages

Dr. Penny Kris-Etherton

DR. KRIS-ETHERTON: The topics I am going to cover are shown on this slide. I will talk about fish recommendations from professional organizations and government agencies, such as FDA.

I am going to just give a real brief truncated version of a talk that I give communicating fish recommendations from both American Heart Association, other professional groups, and FDA, and then we will talk a little bit about effective risk communication principles.

Then, I am going to present a consumer research model developed by the International Food Information Council for communicating food and nutrition messages effectively. Then, we will sum it up.

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A number of professional groups have made recommendations for fish consumption. American Dietetic Association recommends eating two to three fish meals per week to decrease risk of cardiovascular disease. In the late 1990s, ADA published a position paper on women's health and nutrition, and this recommended consuming fish two to three times a week.

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In the year 2000, the American Heart Association released their revised dietary guidelines, and I had the distinct privilege of serving on the Nutrition Committee that developed these food-based dietary recommendations. They differed from other dietary recommendations that were nutrient based in terms of specific percent recommendations.

So, American Heart Association recommends two servings of fish per week to confer cardioprotective effects.

Then, USDA, Department of Health and Human Services, in their dietary guidelines as presented in the Food Guide Pyramid, encourages two to three servings of fish weekly.

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In terms of the fish recommendations made by American Heart Association, as I noted, in the 2000 dietary

guidelines, a fish recommendation was made, and that was published in 2000. There was a science advisory published in 1996 entitled, "Fish Consumption, Fish Oil, Lipids, and Risk of Coronary Heart Disease." Well, a lot has happened since 1996 with respect to fish and health benefits in terms of heart disease, so there is another science advisory in the pipeline, and I am not at liberty to tell you what it says except to say that at least it is in the pipeline, it is going to be published pretty soon, and the American Heart Association took the position of looking at health benefits with respect to heart disease and safety issues with respect to environmental contamination.

So, they balanced a consumer message on the basis of health and risk. That will be coming out somewhat soon.

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As I said, I am going to give just a truncated version of a little talk that I give on fish and cardioprotective effects of omega-3 fatty acids. I have given this talk many times and, as a cardiovascular nutritionist, I am deeply committed to the health benefits of omega-3 fatty acids.

You are going to hear a detailed discussion on nutrition issues tomorrow from Dr. Bill Connor, and this is just sort of the tip of the iceberg of what I present.

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The exact quote from the HA Dietary Guidelines is shown on this slide. "Because of increased evidence for the cardiovascular benefits of fish, particularly fatty fish, consumption of at least two fish servings per week is now recommended."

What is the science evidence that led to this recommendation?

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Well, this particular slide just shows the many, the multiple cardioprotective effects of omega-3 fatty acids in fish, and in particular, I will show you some evidence that shows decreased incidence of sudden death, reduced arrhythmias, antiplatelet effects which protects against thrombosis, marked triglyceride lowering such that omega-3's are used by some physicians in hypertriglyceridemic patients, reduced coronary disease, morbidity and mortality, and what we know is that both alpha-linolenic acid, the plant derived source of omega-3 fatty acids, and marine-based omega-3 fatty acids, EPA and DHA, have cardioprotective effects, higher intakes, about 900 mg/day of EPA and DHA given as a fish oil supplement may benefit patients with coronary disease.

Tomorrow, you are going to hear about striking neurological benefits in terms of the brain, the vasculature, eyes, for fetuses, infants, and young

children. So, again, many, many health benefits of omega-3 fatty acids.

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Here are some of the epidemiologic evidence that we have looked at that we took into account when we made the recommendation for two servings of fish per week. This is from the Physicians Health Study Follow-up from the Harvard Group. It was published in 1998.

What you see here is that with one to two servings of fish per week and more, risk of sudden death is cut in half.

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In a very well-known study, the DART study, which stands for Diet and Reinfarction Trial, a secondary intervention study, it was shown that men with heart disease who were given fish advice to consume between 6 and 12 ounces of fish per week had a much greater survival rate, as you can see, than men who got no fish advice.

In fact, for people who didn't want to eat fish, they were given a fish oil supplement of about 1 gram per day, and those individuals have the same greater survival rate as did individuals who ate fish, showing that the cardioprotective effects are due to omega-3 fatty acids.

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So, given all this, and given the FDA advice, I think that we have to put recommendations for fish consumption in perspective, in the proper context, so that people realize benefits and risks associated with fish consumption.

This is a slide that Bill Harris put together, and this is what we tell people. For pregnant women and women who may became pregnant, the risk for CVD is very low, the risk for methylmercury toxicity is very high, and so the recommendations for fish consumption are to avoid shark, king mackerel, tilefish, swordfish, consume no more than 12 ounces per week of fish low in methylmercury, and select a variety of fish low in mercury and PCBs.

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To deal with other population groups, men under 45 and premenopausal women, they have a moderate risk of heart disease, risk of methylmercury is pretty low, and the fish message for them is consume at least two servings of fish, preferably fatty fish, per week, consume a variety of fish, follow state and federal advisories, and for men greater than 45 years of age and postmenopausal women, who have a high risk of CVD and low risk of methylmercury toxicity, we give them the same recommendations as we do for the younger cohorts - consume at least two servings of

fish, eat a variety of fish, and follow state and federal advisories.

So, this is one way I think of balancing the health message with a risk message, and that is, telling people health benefits and what FDA is recommending.

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Let's talk a little bit about effective communication strategies for consumers. I just want to say two things real quickly on the side.

I have given the talk that I just showed you in more depth to a number of groups to date, and I talked to dieticians and nurses and students, many of whom are non-nutrition majors, and they are very interested in the fish data, and I also talk about FDA recommendations.

I mention those four fish that should be avoided by certain population groups, and they are intensely interested in this, they haven't heard this message before, and I see them writing furiously when I give that message. Many of them come up to me afterwards and want more information about it.

So, I am feeling that the message is getting out, health benefits, but there are these risks because these people now are conduits to consumers. Hopefully, they are getting the message to balance health issues with risk concerns.

Then, one other thing that I do want to say is that because of new processing techniques and plant breeding techniques, consumption of alpha-linolenic acid in the United States is decreasing. Soybean oil and canola oil are rich sources of alpha-linolenic acid, the plant-derived source of omega-3 fatty acids, and a lot of food processors are trying to decrease alpha-linolenic acid in these oils to make these oils more stable and increase their shelf life.

We have actually had an increase in alpha-linolenic acid since the 1970s. We used to eat corn oil and safflower oil, and now that we eat soybean oil and canola oil, the intake of alpha-linolenic acid has increased markedly.

Now, it is going to decrease with these new plant breeding techniques and food processing techniques, and so that door is closing, and consumers need a source of omega-3 fatty acids, and that can be fish eaten in the proper context.

So, let's look at effective consumer messages. I want to talk a little bit about challenges and barriers in communicating risk-benefit messages. You have to keep in mind that people are different. Some understand and want a lot of technical information, and others do not.

So, the current advisory that FDA has, has an 888 number, so consumers have easy access to additional information, somewhat extensive personal control over potential risks and others prefer not to be bothered. They say, okay, FDA is taking care of this, I don't need to worry about it.

Here is where I think there is sort of a double-edged sword here in that often messages are precise and accurate, and they are too complex for most to understand, and yet, on the other hand, simpler messages may be accused of being inaccurate, incomplete, or manipulative, and so somehow we have got to come up with a balance here and communicate effectively with consumers, giving them a message that they can understand quite simply, but then giving them access to additional information.

I think FDA does a wonderful job with that.

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What are some factors that interfere with messages being heard? Well, at the top of the list is credibility of the source, and here is where FDA has no problem with credibility. They are seen by consumers as being a safety net for the public. They are not an advocacy group, they are not a self-serving group.

One other problem that consumers are faced with is inconsistent and contradictory messages across credible

sources. This happens all the time. It happens with professional organizations, and I think we all know about conflicting agency messages, as well.

These are all problems that I think can be dealt with.

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So, how can we overcome barriers? That is with credibility and trust. It is really important to know and target an audience, respect their concerns. I think FDA does a real good job with that in terms of printed guidance with pregnant women. We need to use plain, clear language. Keep messages short, but refer to other references, and there are some people who really do want a lot of additional information, and that can be done using an 800 number or a web site.

DR. MILLER: Dr. Kris-Etherton, you have five more minutes.

DR. KRIS-ETHERTON: Okay.

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I just want to say that it is really important that messages be placed in the proper context.

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We have very good examples where this isn't done. Here is a headline that came out in the local news - "Transfusion fat is unsafe to eat," and this is in response

to a National Academy of Science recommendation saying that there should be no upper limit for trans fat and that the recommended level then is at zero.

Well, we know that it is impossible to eat a healthy diet, for the most part, with a trans fat intake of less than zero, but here is an example where I think a well-intended message got misconstrued, so that with fish, then, it is really important that consumers understand the context of the health message and the risk message.

So, for example, one way that this could go awry is if we say to pregnant women eliminate these fish, well, should pregnant women eliminate all fish, that is one thing that could happen, and then finally it could be misconstrued that everybody should eliminate all fish.

So, we have got to be real careful to get our messages out carefully.

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Just real quickly. Here is an IFIC model for effective communication in health messages.

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Consumers want messages that are positive, short and simple, individualized, specific and manageable, provide a payoff, and they want things to be fun. Life needs to be a lot of fun.

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Here are some examples, real quickly. Be positive. I am going to use an example from the Consumer Advisory from FDA. Seafood can be an important part of a balanced diet for pregnant women. It is a good source of high-quality protein and other nutrients, and is low in fat. A very positive message.

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Crafting tips with consumer appeal. Keep it short and simple. Try a different fish recipe each week. Try many different species of fish.

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Individualize the message. If you love deep-fried fish, try pan-fried fish with just a little vegetable oil.

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Crafting tips with consumer appeal. Here is one that I think is very relevant to the topic at hand. Make it specific and manageable. If you are pregnant or planning to become pregnant, avoid shark, tilefish, king mackerel, and swordfish.

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And then provide the payoff. Follow EPA, FDA, ADA, AHA, USDA guidelines for fish consumption. You will be safe and healthy.

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Finally, make it fun.

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My last slide is a summary. I have shown you significant health benefits of fish consumption, and because of this, the scientific community has made a specific dietary recommendation, however, consumers have to be aware of recommendations of FDA for fish consumption, and they need to know how to balance benefits and risks in implementing these recommendations.

Thank you very much.

DR. MILLER: Thank you.

Questions? Ms. Halloran.

Questions of Clarification

MS. HALLORAN: In your presentation, you mentioned that when you indicated these species of fish, that shouldn't be eaten by pregnant women, everyone takes avid notes.

DR. KRIS-ETHERTON: Yes.

MS. HALLORAN: It was also my experience in preparing for this meeting and mentioning to people what it was about, that it was very much the same, nobody knew that pregnant women weren't supposed to eat swordfish.

DR. KRIS-ETHERTON: Yes.

MS. HALLORAN: I wonder if you know--to me, this is more of negative message than a positive one, that this

message is not getting out and that somehow this is not an effective public health tool, at least as it is being done presently--I wonder if you are aware of or if anybody is aware of information or surveys or research indicating how much of the American public of child-bearing age who is female actually knows about this advice.

DR. KRIS-ETHERTON: I don't know that information, but your point is very well taken because, frankly, with every talk that I have given, at least 10 and probably more than that, it is clear to me that this is news to everybody, virtually everybody.

DR. MILLER: Dr. Dwyer.

DR. DWYER: I have a Boston Naming problem I guess. I don't know what tilefish is. Is there another name for tilefish, does it go by another name?

I guess I know what mackerel is because I am Irish, but what about tilefish, is there a name that people recognize when you give these talks?

DR. KRIS-ETHERTON: Actually, when I say tilefish, nobody knows what it is. It is a fish that is not commonly consumed. I have never seen it in restaurants, I have never seen it in the supermarket.

PARTICIPANT: Golden or white mackerel it is called.

DR. KRIS-ETHERTON: No wonder I have never seen it. Thank you.

DR. RUSSELL: Another question with regard to naming. King mackerel, is there other types of mackerel and does someone have to go in and say is this king mackerel?

DR. KRIS-ETHERTON: I have seen mackerel in the supermarket as mackerel.

DR. RUSSELL: Yes. I have never seen it otherwise differentiated. Johanna, you being Irish, are there several types of mackerel?

PARTICIPANT: There are a lot of types of mackerel.

DR. RUSSELL: Is that the type that would be most commonly in the fish store? I just don't know.

PARTICIPANT: You see Spanish mackerel a lot in the sushi restaurants, that is the one with shiny skin on the outside with the yellow spots.

DR. MILLER: Could you identify yourself for the record?

DR. RAINES: Yes, sir, Ben Raines [ph]. [Off mike.]

DR. BUSTA: Penny, I am assuming that these studies that show increased fish consumption being

beneficial take into consideration that this reduces the eating of other kinds of food.

DR. KRIS-ETHERTON: That is a very good point, and that is another benefit of eating fish is that oftentimes it is a substitute for fatty meat, and so it is a real good way to decrease calories, total fat, and saturated fat.

DR. BUSTA: Is that possibly the main reason it works rather than the fish itself, if you just didn't eat 12 ounces of meat?

DR. KRIS-ETHERTON: That is a very good question, and, in fact, there are a couple of supplement studies out. One is a very famous one, Jissie [ph] study, and it's a long Italian name. It was a very large secondary prevention study where people who had a heart attack got a fish oil supplement every day compared with those that didn't, and with the fish oil supplement, there was a marked reduction in all secondary events.

DR. MILLER: Dr. Fischer.

DR. FISCHER: In the recommendations, it is indicated that if the woman is pregnant or considering becoming pregnant, they should not eat the list of fish.

This tells me that we think that the damage done to development by methylmercury can occur very early,

during the first trimester anyway, right? Now, is there scientific data to back that up, that you know of?

DR. KRIS-ETHERTON: The data that I know of is what happened in World War II, when women were exposed to enormous doses of methylmercury in the early trimester. There were effects at that point, but these were really huge, enormous doses of methylmercury.

So, early on in pregnancy, it can have an effect is my understanding, but it has got to be real large doses.

DR. FISCHER: We heard some reference that the effects were more toward the end of pregnancy, during brain development, that was the critical time, so I am just asking whether these recommendations were based upon firm scientific data.

DR. KRIS-ETHERTON: I guess what I know is, you know, from what happened in World War II, that some women, even in their first trimester of pregnancy, had adverse pregnancy outcome, that's all.

DR. APOSHIAN: Is Dr. Myers still here, because in his review article, I think he--is he here or has he left--in a recent review article, he points that methylmercury has an effect on brain growth during the late period of pregnancy and during the first few years of the person's life.

DR. MILLER: Well, I think in listening to Dr. Kris-Etherton, she is talking about pregnancy outcome, so the influence of mercury was on the pregnancy rather than on the fetus. Isn't that what you were saying, Penny?

DR. KRIS-ETHERTON: Yes.

DR. APOSHIAN: Then, the American Heart Association has not taken a stand on the vulnerability of the fetus to methylmercury in fish?

DR. KRIS-ETHERTON: They really haven't considered that.

DR. DWYER: Is there, in fact, firm evidence that the only effects of methylmercury are on the third trimester of pregnancy?

DR. KRIS-ETHERTON: I don't think so, Johanna, based on what I know about what happened in World War II, but that is my only knowledge of that, I don't know.

DR. FISCHER: I must say I don't know this World War II data.

DR. APOSHIAN: Is that published in the scientific literature, the World War II data?

DR. KRIS-ETHERTON: Let me delve into this a little bit further.

DR. MILLER: Other comments?

If not, thank you.

DR. MILLER: Just to explain to those of you who thought you would see Dr. Schober, Dr. Kris-Etherton has to make a plane, and Dr. Schober agreed to move down one slot.

Our next speaker is Dr. Susan Schober to talk about the NHANES study.

National Health and Nutrition Examination Survey

Dr. Susan Schober

DR. SCHOBER: Good afternoon.

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This afternoon, I will describe the current National Health and Nutrition Examination Survey or the NHANES and present data from the just released 1999-2000 NHANES on blood mercury levels in children and in women of child-bearing years.

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First, I would like to acknowledge that the NHANES mercury component is the result of collaboration with several agencies. In addition to the CDC, my center, the National Center for Health Statistics and the National Center for Environmental Health that did the laboratory work, the collaborators in this component are the Food and Drug Administration, EPA, the Department of Energy, NIH, and the National Oceanic and Atmospheric Administration.

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The primary objective of the NHANES program is to assess the health and nutritional status of adults and children in the United States.

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The analytic and research goals for NHANES are listed in this slide and the next one. These goals are driven by what is unique about this survey, and that is the ability to address public health issues that can best be addressed through physical examinations of the U.S. population.

The goals are to estimate the prevalence of health conditions and related risk factors in the U.S., to describe awareness, treatment, and control of selected diseases, to monitor trends in health and risk behaviors and environmental exposures over time.

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To study the relationship of diet, nutrition, and health, to explore emerging public health issues, and to establish a national probability sample of genetic material.

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The survey is comprised to two parts. There is a household interview and an examination component. The household interview covers a wide range of topics including sociodemographic information, questions on medical history,

health care coverage and need, health behaviors, nutrition, and there are some questions on environmental occupational exposures.

The examination component of the survey is conducted in specially outfitted mobile exam centers. There is an example of one shown in this slide. The topics, the major health topics that we cover in the examination component include cardiovascular disease, osteoporosis, oral health, vision, hearing, balance, fitness and strength, nutrition, anthropometry - there is a whole list, mental health risk behaviors, and environmental exposures and infectious diseases.

As part of the examination, blood is obtained by venipuncture from all participants who are one year and older.

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The NHANES uses a complex sampling strategy to obtain a sample that is nationally representative of the civilian non-institutionalized household population. Persons of all ages and from all states and the District of Columbia are eligible to be included in this survey.

The first stage of sample selection is the selection of counties or primary sampling units, and then within those counties, household segments are selected, and finally, sample persons from the selected households.

It is important to note that within each geographic location where we conduct the study, people are not selected to be representative of that location.

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Beginning in 1999, NHANES became a continuous survey with annual samples representative of the U.S. population. The continuous survey will be released as public use data in two-year groupings or cycles in order to provide adequate sample size for subgroup analyses.

Typically, we go to 15 primary sampling units each year, are selected each year, and the annual sample size is approximately 5,000.

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The NHANES sample design includes oversampling of minority populations and other groups in order to provide reliable estimates for these subgroups. In the current survey, we are oversampling adolescents, older persons, pregnant women, blacks, Mexican-Americans, and beginning in 2000, we also oversampled low-income whites.

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This slide shows the response rate and sample size information for the 1999-2000 NHANES that was just released. We went to 26 locations throughout the United States; 12,160 people were selected to participate in the study, and, of those, almost 9,300 participated in both the

interview and the examination, which gave us a response rate to the examination component of 76 percent.

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The NHANES mercury component was conducted for two subgroups for whom mercury exposure is of particular concern - women in child-bearing years, and in our study, we define that as women 16 to 49 years old, and in children 1 to 5 years old.

As we know from this meeting, the mercury exposure among women of child-bearing age is of particular concern because the developing nervous system of the fetus is most sensitive to the adverse effects of mercury exposure.

Mercury exposure in young children is also of interest because of continuing neurobehavioral growth and development in this period of life.

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Today, I will be presenting information on total mercury concentrations in blood. In the future, there will also be information on hair mercury levels in the women and children, and also on urine mercury levels in just the women.

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The sample size for the children 1 to 5 years old is 705, and the sample size is 1,709 for the women.

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The blood specimens were analyzed for total mercury and inorganic mercury in the Trace Elements Laboratory of the National Center for Environmental Health at CDC in Atlanta. The laboratory used an automated cold vapor atomic absorption spectrophotometry to conduct these measurements. The detection limit was 0.14 mcg/liter or ppb for total mercury, and 0.4 for inorganic mercury.

The inorganic mercury was non-detectable in 98 percent of the sample, and I will only be presenting information for total mercury.

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The distribution of blood mercury levels in children and women for this presentation are described through the calculation of percentiles in geometric means. Sample weights were used to account for the complex survey design, the oversampling, and for non-response.

Standard errors are calculated with a statistical package of programs called SUDAAN, which accounts for the complex survey design.

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The mercury component also includes questions about fish and shellfish consumption. Survey participants or its proxy respondents for the children were asked about fish and shellfish consumption during the past 30 days.

They answered questions about fish and shellfish separately.

The basic question is: "During the past 30 days, did you eat any types of fish listed on this card? Include any foods that had fish or shellfish in them, such as sandwiches, soups, or salads."

The list of fish and then also the list of shellfish included other and unknown categories, as well as specific species.

These questions were asked after respondents had completed a 24-hour dietary recall that is conducted in the mobile exam center, so there is also information from the 24-hour recall about fish consumption.

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The geometric mean concentration of total mercury in blood was 0.3 mcg/liter for the children 1 to 5 years old, and approximately 1 mcg/liter in the U.S. women 16 to 49 years old. We can see from this that the blood mercury levels were approximately 3-fold higher in the women compared to the children.

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This slide shows the cumulative distribution of blood mercury levels in the children and women, so it is showing the percentiles on the X axis, and the blood mercury levels in mcg/liter in the Y axis.

One can see from the graph that the difference between levels of women and children is greater at the upper percentiles.

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I actually show the numbers for the upper percentiles, the 90 at the 95th for women and children. The confidence intervals around those estimates are in parentheses and I see that in the 95th percentile, it goes over to the left.

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Blood mercury levels were positively associated with fish consumption in the past 30 days. This graph again shows the cumulative distribution of blood mercury levels, and this is for women for three categories of fish consumption - those who ate no fish in the last month, those who ate one or two servings, and those who ate three or more servings.

Blood mercury levels increased with the fish meals consumed. The pattern was observed throughout the distribution from the lowest to the highest percentiles.

I don't have a slide for this, but the geometric mean mercury levels were almost 4-fold higher in the women who ate three or more servings of fish in the past month compared to women who ate no fish in that time period

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Here, I show the cumulative distribution for fish and shellfish consumption together to sort of examine how we need to look at this. I understand that there can be some exposure to mercury from shellfish, but what we see in this slide is that women who ate both fish and shellfish had the highest mercury concentrations compared to women who ate only fish or shellfish.

This could be related to the fact that women who eat both just eat more, and the women who ate only shellfish had slightly higher levels than women who ate neither fish or shellfish during the past 30 days.

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Among women 16 to 49 years, I have already shown that the 90th and 95th percentiles for blood mercury concentrations were 4 and 7 mcg/liter respectively.

In 2000, we have already heard discussion of the National Academy of Sciences committee report. They recommended a lower limit benchmark dose or BMDL modeled from the Faroe Island study of the developmental effects of in utero exposure.

The BMDL that was recommended was 58 mcg/liter. I am comparing the NHANES results to just the NAS recommendations, not to other effects or risk levels that have been identified by other groups.

In order to account for the uncertainties of exposure measures and the variability in individual response to toxic effects of mercury, the National Academy of Sciences committee further recommended using an uncertainty factor of 10 to calculate the reference dose.

This corresponds to a concentration of 5.8 mcg/liter of mercury in cord blood.

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In the NHANES, 1999-2000, there were no women who had blood mercury concentrations at or above the BMDL of 58 mcg/liter. The highest blood mercury concentration that we measured in this sample of women was 39 mcg/liter.

But if you look at the proportion of women whose mercury levels were at the value of 5.8 or higher, that proportion is 7.8 percent. The confidence intervals around that estimate are from 5 percent to 10 percent.

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On this slide, I have listed a couple of limitations of the NHANES with regard to providing information on mercury exposure in the U.S.

First, the NHANES samples was not designed to oversample subgroups within the U.S. population, who are frequent consumers of fish or who might be frequent consumers of fish, so it was just sports fishermen or certain American Indian or Alaskan Native groups, or

population groups who may have higher mercury exposure because of geographic location.

Related to this point, it is not possible to examine geographic variation in mercury exposure in this study, and this is partly because we didn't oversample based on geographic location, and also we do not provide geographic information in the public release data because of statistical disclosure issues.

Finally, even the sample sizes might seem quite adequate, they are still quite small for subgroup analyses that people might be interested in.

DR. MILLER: Dr. Schober, you have five minutes.

DR. SCHOBER: Thank you.

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The major strength, of course, of the NHANES is that the survey provides estimates that are representative of the general U.S. population. In the case of the mercury measures, we just did it in these two age groups, so these are representative of young children and women of child-bearing age.

These estimates may be used as a reference for studies conducted in other communities or groups who might have potentially higher exposures.

As we continue to measure blood mercury levels in future years of this study, these data will allow

examination of secular trends to evaluate continuing efforts to reduce mercury exposure in the United States.

This survey also provides sociodemographic information, as well as fish and shellfish consumption information that may be examined in relation to the blood mercury levels.

In conclusion, the NHANES measures of mercury exposure in women and children are well below the levels considered hazardous from the epidemiologic studies, however, almost 8 percent of women had blood mercury levels at or above the cord blood concentration that corresponds to the reference dose recommended by the NAS committee.

This is a level that takes into account uncertainties in measurements in the epidemiologic studies and variation in individual response to the adverse effects of mercury.

I hope that these NHANES data will be useful to the FDA, the Food Advisory Committee, as well as other groups in developing the best advice for pregnant women and women of child-bearing age about the inclusion of fish in their diet.

Fish is a nutritious food. We have heard that from the last speaker, and we don't want to tell women not to eat any fish at all.

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My last slide shows the web site for NHANES where one can go for more information about the study, the survey, as well as to find the link to download the data that we just released from the 1999-2000 survey.

Thank you.

DR. MILLER: Thank you.

Comments or questions from the committee?

Questions of Clarification

DR. HOTCHKISS: I just wanted to make sure I understood. The NHANES population that you are talking about, particularly the women in here, you would consider representative of the U.S. female population in large, but not representative of any subpopulation of that group, am I correct in that assumption?

DR. SCHOBER: It is representative of the U.S. population in total, but we cannot say anything about within the U.S. population smaller groups. We couldn't make separate estimates for groups that might have a higher level of exposure because of more frequent fish consumption. That is beyond what is the average in the U.S. population.

DR. HOTCHKISS: Then, the assumption that 8 percent of the female U.S. population would have a blood level above 5.8, which thumbnail I calculate out about 11

million women in the U.S. probably have a blood level above that level, is that correct?

DR. SCHOBER: I didn't actually look at the number of women, but it would be--

DR. HOTCHKISS: If you consider there are 280 million residents and roughly half of them are women, I think probably it is a little more than half.

DR. SCHOBER: We can actually get that figure exactly from our analysis.

DR. HOTCHKISS: So, it would roughly be 11 million give or take a few probably.

DR. BUSTA: This is the first time I have heard shellfish mentioned. I know we have been talking about fish, and I am not sure that we have included shellfish in this activity.

Did you do much differentiation about shellfish and fish, the way it is prepared, what types, any kind of other specifics?

DR. SCHOBER: We didn't. In this analysis, is it just looking at any shellfish at all in the past 30 days.

DR. BUSTA: And any fish in the past.

DR. SCHOBER: And any fish except for that first slide where I had the three levels of fish consumption, but that was in the past 30 days.

DR. MILLER: Dr. Shannon.

DR. SHANNON: I have actually more than one question, so you will have to tell me when my time is up.

My first question is I wonder why the mercury isn't speciated. We are here to discuss methylmercury, but only total is being measured, and, for example, I think about either measuring mercury in children during a time when they are getting so many immunizations, and you can't tell us if the mercury you are measuring is methyl or from the thimerosol or what the source is.

I am sure your lab has the ability to do that speciation, so why wouldn't it?

DR. SCHOBER: As I understand, the lab has, at least during the time period for these two years, had the ability to do the speciation to measure inorganic mercury. Inorganic mercury is best measured in urine rather than in blood, so the inorganic mercury levels were below the limit of detection for the majority of the women and children in the sample, so we feel that the total mercury is a good indicator of methylmercury.

DR. SHANNON: But it wouldn't be in a child, right?

DR. SCHOBER: I am not sure about that part of it.

DR. SHANNON: And if you look at children between 1 and 5, and you are measuring mercury, you don't really--I

think it is more likely to be from ethylmercury and thimerosol than it is from methylmercury and eating fish in a 1 to 5-year old.

DR. SCHOBER: I don't know what the laboratory plans are for further speciation particularly in the children.

DR. SHANNON: Am I able to ask another question?

DR. MILLER: Go right ahead.

DR. SHANNON: One of the advantages of the old NHANES methodologies was that even though it took longer, there was large enough sampling that you could produce more accurate estimates of prevalence.

So, for example, the data that we still hear about, the prevalence of childhood lead poisoning is based on the 1991-94 data, and in doing annual surveys with such a smaller sample size, the best we can do is what you have given us here, are some 95 percent confidence intervals.

So, I am wondering if there is any type of plan to take advantage of what the old NHANES offered in terms of giving us prevalence data that we can feel comfortable with.

DR. SCHOBER: The survey is now continuous, so we will be putting data out into your groupings. The next data release will be data for 2001 and 2002, and then the two, two-year releases can be combined for four years of

information, which would provide larger samples sizes for some of these smaller groups in the lower prevalence, estimates that are of interest.

DR. SHANNON: Just finally, a comment more than a question. I wonder and worry about the value in looking at the blood mercury in women and extrapolating it to a cord blood mercury. Do we really know enough about the kinetics of methylmercury to feel that what you have in terms of blood mercury really is going to accurately reflect what the cord blood would have been?

DR. SCHOBER: I am not an expert in that at all, but I do believe from the literature that there are different estimates of the correspondence between what would be measured in cord blood versus maternal blood.

In some cases, I have heard there is a 1 to 1 ratio, in other cases I have heard--and I hope I get the direction correct--that it is a 1 to 2 for maternal to cord blood--or 20 percent higher, actually, not 1 to 2, but 20 percent higher.

MR. CLEWELL: Anywhere from the same to 2 times higher in the cord blood.

DR. MILLER: Dr. Dwyer.

DR. DWYER: Thank you. I was interested in the probe after you ask have you had fish in the last 30 days

or shellfish, and then you show them a card with all of these different names of fish on it.

DR. SCHOBER: Yes.

DR. DWYER: Do you have the names of the fish that you asked for, or could you make it available to us?

DR. SCHOBER: Yes, I could do that.

DR. DWYER: Thank you.

DR. MILLER: Dr. Nordgren.

DR. NORDGREN: The slide with the three different groups of consumption, could you repeat those?

DR. SCHOBER: The lowest was no fish consumption at all in the past 30 days. Then, it was one to two fish servings in the past 30 days. Then, three or more fish servings in the past 30 days.

DR. NORDGREN: So, this is 30 days versus the recommendation that we have for twice a week.

DR. SCHOBER: Right.

DR. NORDGREN: Two servings per week.

DR. SCHOBER: The reason I showed the data the way I did, I was interested in showing the cumulative distribution, the upper percentiles.

The sample size for women who ate fish twice a week or eight times in the past 30 days or more is 99, and that is getting to be a pretty small sample size to be looking at these distributions.

DR. MILLER: Dr. Friedman.

DR. FRIEDMAN: I am interested if you have in the dataset in general, not the part that you presented today, demographic information about the women and the developmental data about the children.

DR. SCHOBER: We have some demographic information about the women, but not developmental information about the children. It's a cross-sectional study. You mean the children--

DR. FRIEDMAN: Assessment. It could be cross-sectional.

DR. SCHOBER: You mean the children 1 to 5.

DR. FRIEDMAN: Yes.

DR. SCHOBER: I don't think we do this time, no, we don't. We have done the WISC rat in the previous survey, but we are not doing that currently.

DR. FRIEDMAN: Thank you.

DR. ACHOLONU: You showed that in your studies you used blood level of mercury. Some people have done some work and have shown that the two major target organs for long-time exposure to mercury is the nervous system and the kidney, which means that we should be testing urine.

Why is your work limited to blood, why have you not checked urine? And if you have not, why have you not done the urine samples?

DR. SCHOBER: I didn't speak comprehensively about everything that we do in the survey. We do a very large number of laboratory assessments. We do collect urine samples. I know that there is a couple of tests that we do in the urine, samples that might speak to kidney dysfunction. I can't say exactly what those might be.

We could look at that. One would have to keep in mind that this is a cross-sectional study and we are looking at current exposure, and it would a current assessment of kidney dysfunction. We wouldn't be able to say anything about the exposure over the lifetime of the person.

DR. NORDGREN: Can I respond to that question?

DR. MILLER: Yes, sure.

DR. NORDGREN: It would be very hard to do urine because mercury levels in urine would be pretty meaningless unless it was a 24-hour urine because the urine is so diluted and concentrated, so if you are measuring mercury at levels in a spot urine check, it would be pretty meaningless versus doing a 24-hour urine.

DR. SCHOBER: Excuse me. I misunderstood the question. I was thinking that you were referring to tests that would be reflective of kidney dysfunction in the urine. We are measuring mercury levels in urine, but I

wouldn't think that that would be an indication of known effect on the kidney, and it is a spot urine.

DR. APOSHIAN: I think, going back to mercury in the urine, that that is still one of the classical ways of detecting mercury toxicity by doing a creatinine that goes along with it. So, spot urines are perfectly acceptable in the toxicology community.

DR. SCHOBER: We do do creatinine correction for our urine assessments.

DR. APOSHIAN: But urine mercuries are usually considered to be indicative of long-term exposure, whereas, as you said, blood mercuries are indicative of short-term or recent exposure.

DR. NORDGREN: I thought he asked mercury levels in the urine. I thought that was the question.

DR. APOSHIAN: Mercury levels can be done relatively routinely, automatically now. Most labs can get down to 2 mcg/liter without any trouble whatsoever. I see mass spec and other techniques, and even with the cold vapor method of determining mercury, you can get down to about 2 mcg/liter if it is a good laboratory.

DR. NORDGREN: But that is on a one sample. If you are measuring--the concentration in the urine depends how dilute the urine is. So, if you drank a gallon of water just before you gave your sample--

DR. APOSHIAN: But that is why the creatinine is done.

DR. NORDGREN: Right.

DR. APOSHIAN: So, if you base your data on the creatinine concentration, it does away with the dilution factor.

DR. SHANNON: Isn't the primary issue, though, that methylmercury is not excreted in urine, the primary route of excretion for methylmercury is bile, so we wouldn't be that interested in measuring mercury in urine anyway if we were interested in the extent of methylmercury exposure.

DR. MILLER: Any other comments or questions?

If not, thank you.

The next speaker is Ms. Caroline Smith DeWaal from CSPI to talk about Risk Management Strategies for Methylmercury in Seafood - A Consumer Perspective.

Risk Management Strategies for Methylmercury in Seafood - A Consumer Perspective

Ms. Caroline Smith DeWaal

MS. SMITH DeWAAL: Good afternoon. I want to thank FDA for inviting me. I also want to apologize. We had a major outbreak and recall last Friday, which has kept me fully occupied, and I do not have a PowerPoint presentation, so I apologize.

Leora Begosin, however, is going to hand out a petition and also consumer advisory that we have prepared that is part of my presentation, and, in addition, probably tomorrow or the next day, we will get you copies of the actual presentation.

CSPI is supported by 800,000 consumers in both the U.S. and Canada, and we are totally independent. We don't accept government, industry, or even union contributions. We are really supported by consumers.

Methylmercury in seafood is not a new issue to the Food and Drug Administration, but luckily for the public, it is one that is getting increased attention. I apologize in advance if my talk seems somewhat like a history lesson, but this is a topic that I have been working on since the early 1990s, and there is a lot of history that I don't think this committee has gotten yet.

The Food Advisory Committee is being asked to evaluate whether FDA's Consumer Advisory on Methylmercury is adequate to protect the health of those who follow the advice.

To answer this question, I believe that the committee must first be satisfied that the FDA's standard or action level is sufficient to protect vulnerable consumers. This is the same standard that the National Academy of Sciences harshly criticizes in 1991 with the

publication of a report called Seafood Safety, which I don't believe has been discussed yet at this meeting.

Second, the committee should evaluate the appropriateness of placing the entire burden for preventing the adverse consequences of methylmercury in seafood on the consuming public. This committee should explore the issue whether FDA should be more proactive in preventing the most highly contaminated seafood from reaching the marketplace especially given the current status of the at-risk population and the failure of FDA's past seafood safety policies in addressing methylmercury.

In 1999, we got the first glimpse of the current levels of consumer exposure to methylmercury in the NHANES study, the data which has just been presented.

This study showed that 1 in 10 women of child-bearing age in the U.S. are at risk of having babies with learning disabilities or other developmental defects because of in-utero mercury exposure, primarily through fish consumption.

This data shows, gives real-time measurement of the effectiveness of current risk management strategies in protecting women of child-bearing age from accumulating levels of methylmercury that may have adverse effects.

Unfortunately, the structure of the federal food safety regulatory system is fragmented and it is ill equipped to meet this challenge.

Two federal agencies, the Food and Drug Administration and the EPA, both have regulatory authority over this issue, and a third federal agency has an additional standard which we have heard about today, the Agency for Toxic Substances and Disease Registry, the ATSDR.

All three agencies have established standards for human exposure of methylmercury from fish and shellfish, but none of the standards agree on what level of methylmercury represents a threat to consumers.

The FDA has primary authority for regulating seafood that is in the marketplace, that is commercially sold, and it is most of the seafood that is being consumed by the U.S. public.

Using its public health mandate, the FDA established an action level of 1 part per million for mercury-contaminated commercial seafood. For recreationally caught freshwater fish, however, that standard doesn't apply, and EPA has issued its own methylmercury guideline under water pollution laws.

The EPA's water quality criterion is based on the Agency's reference dose for mercury, which is 0.1

mcg/kilogram/body weight/day. I think we have heard this already, this is the daily exposure of the human population including sensitive subgroups that is likely to be without appreciable risk of deleterious effects during a lifetime.

In simpler terms, a reference dose represents the daily dose of a substance that would be acceptably safe even to sensitive subgroups. So, in the case of mercury, EPA's reference dose is designed to account for effects on the developing fetus.

In addition, we have already heard about the ASTDR standard, which has its own standard of 0.3 mcg/kilogram/day. Ironically, the most protective public health standard is the one put forward by the Environmental Protection Agency, and not the one put forward by FDA.

FDA's action level of 1 part per million for mercury in fish was calculated only to protect adults. It was not developed with the consequences to the fetus in mind, and I will go into that later in my paper.

In terms of human exposure, and it is difficult to make all these numbers fit, but the FDA's action level translates to 4 mcg/kg/body weight/day. So, EPA is at 0.1, ASTDR is at 0.3, and FDA is at 0.4 mcg/kg/body weight/day, which is four times higher than EPA's reference dose.

Unfortunately, for pregnant women and their children, the seafood sold in supermarkets and restaurants

is regulated under FDA's weaker standard. Moreover, the FDA's action level is only an informal enforcement policy, and it is not legally binding either on the Agency or on the seafood companies.

More importantly, it does absolutely nothing to prevent heavily contaminated fish from being sold to consumers. FDA's action level on methylmercury is truly a toothless tiger.

What FDA has done in response to the mounting evidence about the inadequacy of its standard is to issue a consumer advisory, placing the burden firmly on consumers to protect themselves from the risks that this toxic agent in seafood poses.

In January of 2001, FDA issued a press release telling women who are or may become pregnant not to eat shark, swordfish, king mackerel, and tilefish due to likely contamination. These women were told that it was safe to eat up to 12 ounces per week of other types of cooked fish, no warning. The warning was silent on tuna.

The FDA advisory also states that it would be prudent for nursing mothers and young children to follow the same recommendations as women who may or are pregnant, may become or are pregnant.

FDA's decision to regulate by press release has been highly ineffective and here are a few reasons. First,

there was major rollout of the new advisory. There weren't public meetings, there wasn't a press conference. There is also no labeling or retail display programs as part of this program.

Second, many consumers who need to hear the advisory are very likely to actually hear it. Media outlets frequently don't reach people who don't speak English as a primary language. Moreover, half of all pregnancies are unplanned, so to reach the appropriate audience, the message really needs to be directed to all women of child-bearing age.

FDA's advice is so incomplete that several other consumer and public health groups have developed competing advice in order to fill this void. CSPI issued its own advice in the Nutrition Action Health Letter, which goes to our 800,000 members back in September of last year, and we have very specific recommendations for young children about tuna consumption, an area where FDA has been notably silent.

In addition, Consumer Reports magazine has issued their own consumer advice including young children, and Environmental Working Group has another piece of advice and has listed many more types of fish. I know you will be hearing from Richard Wiles tomorrow.

At the same time that FDA came out with its new consumer advisory, EPA issued a national consumer advisory on recreationally caught freshwater fish, and EPA recommended that women who are or may become pregnant or nursing mothers should eat no more than 6 ounces of cooked freshwater fish per week, and young children should eat no more than 2 ounces of cooked freshwater fish.

Although EPA's guidance covers different fish species, for most consumers, they were hearing a conflicting message - should I be eating 12 ounces of fish, 6 ounces of fish. It is very difficult to communicate clearly when we have all these competing messages coming out of the government.

Fundamentally, one of the problems that exists is the advisories for recreationally caught fish are put out by the states and local governments. They get to pick and choose which standard they use. So, you can have one state using the FDA standard, you can have another using the EPA standard, even some states using more protective standards, some using the Canadian standard, which is more protective than FDA.

So, again, consumers are getting messages that are competing and are not clear because of these problems with the federal standard for methylmercury.

What is the response to all these conflicting messages coming from the government? I think consumers learn to mistrust the government messages and also there is huge confusion. People really don't know what advice to follow.

The result is a loss of confidence that the messages that are coming out of the government are really truthful. We think one of the responses to this, and a critical response, is to have an actual enforceable standard for methylmercury and seafood that FDA enforces.

The current action level was first issued as an administrative guideline for fish in 1969 in response to the Minamata outbreak. At that time, the Agency set the permissible level of mercury at 5 parts per million--0.5, 0.5 parts per million.

FDA converted this standard to an action level in 1974, recognizing that chronic exposure to fish and shellfish containing methylmercury poses a greater potential for danger to women of child-bearing age than to the general population.

So, in 1974, they recognized that pregnant women were an important subgroup to consider, but in later action, FDA ignored this critical public health consideration. Following litigation challenging its mercury action level, in 1979, FDA relaxed the mercury

standard to 1 part per million because of new information on consumption and socioeconomic impacts presented by the National Marine Fisheries Service.

According to FDA, NMFS, National Marine Fisheries Service, concluded that--and I am quoting here--"The higher level would provide a significant economic benefit to those industries most seriously affected by regulatory actions under the 0.5 part per million guideline."

In 1984, FDA revised the 1 part per million mercury action level again, so that it applied only to methylmercury. In doing so, FDA acknowledged that the revision of the action level might result in increased consumer exposure to methylmercury, but concluded that this increase in exposure will not be a public health concern.

Despite the recognition by FDA in 1974 that exposure to methylmercury might harm fetuses, no allowance was made in setting the action level and in revising this action level to provide protection for pregnant women and children.

Later decisions in 1979 and 1984 that increased exposure to mercury never revisited the issue of fetal effects. It should not be surprising then that when the National Academy of Sciences issued its seafood safety reports in 1991, it extensively criticized FDA's

methylmercury action level for not adequately protecting pregnant women and children.

Most notably, the NAS criticized FDA for basing its standard on the lowest blood level of mercury reported to produce effects, the LOAEL, not the NOAEL, rather than its typical approach of using the no observable effects level.

Additionally, NAS pointed out that the FDA standard failed to account for two critical variables, the well-documented differences among individual rates of mercury elimination and among the fetal response to mercury exposure.

The NAS concluded--and I am quoting--"Although the 10-fold safety factor as applied appears to offer a reasonable degree of protection for adult effects, projections of the fetal dose-response data suggest the possibility of appreciable risk from methylmercury exposure even at levels to which many people are exposed via their diet."

FDA did nothing to respond to this damning report. Based on the mounting evidence of flaws in FDA's mercury action level, in 1992, I petitioned FDA on behalf of a consumer organization to establish a regulatory limit for methylmercury in seafood that would protect pregnant women and children.

There were two significant components to this petition. First, we sought more stringent standards that would account for the fetal effects, but equally important, it asked FDA to set a regulatory limit rather than just an action level.

An action level identifies the level of contamination above which FDA may bring enforcement action. At best, an action level is a yellow light for the industry signaling when FDA may consider a food to be adulterated, but each time FDA brings a case to remove seafood on the basis of that action level, it must prove the threat to public health caused by the seafood in question. You have to bring the same case over and over again.

A regulatory limit, by contrast, is a red light. It signals to the industry that it cannot sell seafood that exceeds that limit. It is a legally enforceable standard that is binding both on the Agency and on the industry.

It eliminates the need for FDA to justify and rejustify its action level in every separate case. Unfortunately, FDA never responded to this petition.

During the 1990s, much of the public debate over mercury centered on EPA's efforts to clamp down on mercury emissions from fossil fuel-burning power plants. The issue of mercury-tainted fish was never far from the spotlight,

however, since Congress had asked EPA for a report on the health effects of such emissions.

DR. MILLER: Caroline, five minutes.

MS. SMITH DeWAAL: Five minutes? Thank you.

In its mercury study report to Congress in 1997, EPA estimated that between 1 and 3 percent of women of child-bearing age eats sufficient amounts of fish to be at risk for methylmercury exposure. We now know that to be an underestimate.

EPA also reaffirmed its 1 mcg/kg standard as protective of brain development in young children. EPA's report was not well received, however, and so Congress instructed EPA to commission another NAS study on the appropriate reference dose for methylmercury.

The new NAS report was released in July 2000 and garnered significant media attention. The 2000 NAS committee endorsed EPA's mercury standard of 1 mcg/kg/body weight/day.

NAS said EPA's reference dose is "scientifically justifiable for the protection of public health." Of particular note, the NAS estimated that over 60,000 U.S. children are born each year at risk or neurological problems due to in-utero exposure to methylmercury.

What got little attention in the report was the committee's call for harmonization of the mercury standard

among the different agencies, and as the earlier NAS report found, several of the panel's recommendations, when applied to FDA's action level for methylmercury, revealed fatal flaws in FDA's standard-setting process.

Specifically, the 2000 NAS panel found the following: There is a strong database of human and animal studies showing neurotoxic effects, but that these are not included in the basis for FDA's current action level.

Second, the NAS said that the developmental neurotoxicity should be the endpoint in calculating the appropriate regulatory level for methylmercury, but FDA has used overt neurological symptoms in adults as the endpoint, therefore, its action level is set to protect adult men weighing 154 pounds and over.

Third, the NAS recommended a benchmark limit of 58 parts per billion in the cord blood, which corresponds to approximately 12 parts per million in hair, but FDA's standard is approximately four times higher than this.

This report added to the large body of science showing the adverse effects of low level methylmercury exposure on the developing fetus, and since then, CSPI has resubmitted our petition asking again for FDA to take action.

More than a decade has passed since the first National Academy of Sciences' report criticized FDA's

standard for failing to offer adequate protection especially for the unborn. A full decade has passed since consumer groups first petitioned FDA to address this flaw.

Consumers should not have to continue to wait. We have waited through the publication of two National Academy of Sciences' reports, which essentially reached the same conclusion, for the FDA to take action to protect our health and our children.

We have a mountain of evidence today supporting our call for a more protective standard for methylmercury in seafood, and we hope that this committee will help move the Agency in the direction of setting an enforceable standard.

Thank you.

DR. MILLER: Thank you, Caroline.

Comments, questions?

Questions of Clarification

DR. APOSHIAN: If there are no questions, I would like to make a comment and a request. From the reading that I have done, especially on Sunday, there is a report put out by the General Accounting Office--is that what it is called, GAO of the U.S. Government.

It is dated January 31st, 2001. It is a critique of the FDA's Seafood Safety Program. It is GAO-01204. Could the members of the committee get an executive

summary, a copy of the executive summary of that report? Is that possible, because I think it would be valuable for us especially in light of what was just said in criticism of the FDA to see what the General Accounting Office's comments were. Thank you.

DR. DICKINSON: Caroline, I saw your petition on the web materials that were provided for us here. I believe you asked for an actual action level or limit or regulatory limit of 0.1?

MS. SMITH DeWAAL: No, 1 part per million is the current standard. We considered asking for--actually, no, you are right, the cover letter to the petition this time asked them to use the EPA reference dose as their new action level while they set a formal regulatory limit.

DR. DICKINSON: And that would be 0.1.

MS. SMITH DeWAAL: Yes.

DR. DICKINSON: Micrograms per what?

MS. SMITH DeWAAL: Micrograms per kilogram.

DR. DICKINSON: Per kilogram of?

MS. SMITH DeWAAL: Body weight. The problem is they have got to transfer that back to allowable level in fish.

DR. DICKINSON: And what, in your view, would be that level?

MS. SMITH DeWAAL: It would probably be 0.25.

DR. DICKINSON: And we have been given a number of tables.

MS. SMITH DeWAAL: That is 0.25 part per million.

DR. DICKINSON: Parts per million, right. We have been given 0.25 parts per million, right?

MS. SMITH DeWAAL: 0.25.

DR. DICKINSON: We have been given a number of tables on mercury levels in fish, and a substantial number of the samples do appear to exceed that level.

MS. SMITH DeWAAL: Yes.

DR. DICKINSON: What would be your comment on the impact of that?

MS. SMITH DeWAAL: Well, I think, number one, it would allow them to make consumer advice that is more consistent and more health protective than the advice they have today, but in addition, the data that you have on the amount of mercury in fish is quite flawed. It is based on some data that was collected, some of it 20 years ago, 30 years ago.

There has been ongoing investigation of this by a newspaper down in Alabama, the Alabama Register, and they found significant amount of methylmercury in a number of species that aren't even listed by FDA.

They also note that the U.S. Commerce Department has admitted that the data that FDA is using today to

analyze methylmercury concentrations in seafood is seriously flawed, and I believe they are doing a new study, a new seafood fish study to determine what are appropriate levels.

DR. DICKINSON: Without regard to exactly how old this data is, because I think we do have some newer data here, what is your comment if the result of that is to basically put out of bounds a large fraction of the current seafood supply?

MS. SMITH DeWAAL: Well, first of all, I think the first question this committee needs to look at is regarding the consumer advisory and whether the basis, the 1 part per million standard should be the basis for that consumer advisory.

I think you need to have a more protective standard in order to evaluate the fish that are taken in as part of that consumer advisory.

Secondly, there are some species of fish which will never come within the legal limit. I believe that some species of shark and there are probably some species of swordfish which are regularly exceeding that limit.

I think they need significant warnings. You know, we are basing these advice on the average consumer, but realistically, people who eat swordfish, eat it over

and over again. People who eat shark, eat it over and over again, and most of us never eat it.

So, I think we need to be realistic about who the consumers are, and there may be some species of fish which shouldn't be sold commercially. They could still be recreationally caught perhaps, but they shouldn't be sold commercially if they can't meet government limits.

DR. SHANNON: I have for you, Dr. Miller, a question of process. You gave us five specific charges and questions we are here to address, and the issue that has come up here is both the maximum daily intake that the FDA uses of 0.4, should that be revised, and the issue of whether the FDA should be thinking about a regulatory action.

Neither of those are part of the five questions. Should we, as the committee, therefore assume that we are not going to touch that?

DR. MILLER: No, I think there are issues. We want to concentrate on the five questions, because that is the questions the Agency asked us to respond to, but the question of the dose level, I think is one of the questions, it is included in one of the questions.

All of these issues have to be determined if you are going to try and answer the questions.

DR. RUSSELL: You didn't speak too much about the ATSDR advisory, which I think their conclusion was that the level should be set at 0.3 mcg/kg/day.

As I look at that study, looked at the way they did it, they used the Seychelles study as the lead study or the critical study, whereas, the National Academy, as I look at their summary, I don't have the whole report, but as I look at the summary, is the Faroes study is the critical study.

So, it is judging the science, I guess--see if I have got this right--it is two different committees, each feeling, one feeling that the science that should be emphasized in one analysis was different from the other analysis, so it is sort of a scientific disagreement, I gather. Is that correct?

MS. SMITH DeWAAL: Yes, and I think there are two points I would make on this question. The first is that there are actually two studies that show adverse effects. One is the Faroe Islands, but the other is the New Zealand data.

So, I think you have to look also at the New Zealand study because that should be weighted into this decision of which study to use. But the other thing is the Faroe Island study--and I attended the meeting down in Raleigh, North Carolina, where all the scientists from both

studies, and actually, it was about four studies, got together to compare their studies--and clearly, there is a confounder in the Faroe Island study because of the presence of PCBs in that study, that is probably not in the fish in the Seychelles Islands.

But a key consideration is in the U.S. population, we probably have similar consumption of PCBs in the seafood, so if there is a synergistic effect because of those two chemicals in the diet or in the fish at the same time, that may also be happening in the U.S. population.

So, again, this is difficult because they are both well-designed studies, they are both by very excellent researchers and groups of researchers, but I think you need to figure out what best applies to the U.S. population.

I will note that under the Food Quality Protection Act, which isn't applicable here, but it will tell you where Congress is going with that, they have told EPA to consider the synergistic effect of different chemicals in our diet.

So, that is something that is currently going on at EPA in terms of their analysis of pesticides, and I think chemical residues in seafood is an extension of that analysis.

DR. HOTCHKISS: We have heard and I think most would agree that there is good evidence for positive health

benefits from consuming seafood products, and I think it is reasonable to expect that any restriction in the standard for methylmercury or mercury compounds in fish will either drive up the cost or reduce the availability of seafood products.

Are you concerned that this may, in fact, have a negative health benefit for the U.S. population rather than a positive?

MS. SMITH DeWAAL: Well, I think we are talking about different types of fish. I mean there are over 300 species of fish for sale in the U.S. There is a huge variety of fish. Some of them have methylmercury, a lot of them don't. The ones that have methylmercury tend to be predatory fish, they tend to be at the top of the food chain.

You know, consumers could reduce their consumption of swordfish and shark and even fresh tuna steaks, and probably fill in with other species of fish that don't raise this problem. So, I don't see it as an either/or issue.

DR. MILLER: Dr. McBride.

DR. McBRIDE: I sense your concern about this issue, and perhaps we are not here to address the question of a regulation, but does your organization take a stand on the availability of cigarettes for the pregnant woman?

MS. SMITH DeWAAL: The availability of cigarettes?

DR. McBRIDE: Should they not be sold because they are toxic to pregnant women?

MS. SMITH DeWAAL: We haven't worked on that issue. I don't know what our formal position would be. I mean there are specific warning labels on cigarettes that deal with pregnancy and on alcoholic beverages that deal with pregnancy.

I don't see specific warning labels on seafood products for pregnant women.

DR. McBRIDE: Might that not be an alternative to regulation?

MS. SMITH DeWAAL: As long as the science is good and the data is good about which species of fish are actually the ones that are most at risk of causing harm including recommendations on tuna and other things, yes, warning labels might be a risk management strategy.

DR. MILLER: Dr. Montville.

DR. MONTVILLE: Dr. Miller mentioned this morning when we started that science is an important component of policy, but not all of it, and while we discussed the numbers, whether they should 0.1 or 0.4, I am really struck by Dr. Hotchkiss' comment and yours that 1 in 10 women are over the current standards, so we have 11 million women

over the current standard, and I don't think whether we lower it to 0.1 or 0.01, will have much effect on that.

As a consumer activist, how can we get that word out and make it more effectively received, so that we have the end product we want, which is fewer women going over the limit?

MS. SMITH DeWAAL: I have struggled with that question because this is, as I said when I started, this is something I have been working on for about 10 years with very little success.

But one concept is the fish we are talking about tend to be pricey, they tend to be top end. Now, there is a whole issue about recreationally caught fish and subsistence, people who are fishing to actually provide protein for their families, but for the FDA model, we are really dealing with fish that are top-end fish.

You know, perhaps there is a way to get the message out to those consumers who tend to be--you know, I mean women who are anticipating becoming pregnant tend to be information seekers.

We are trying to get consumer messages out to him on listeria already, I mean so there might be a way to do this, but the NHANES data clearly shows that the risk management strategies in use today are not working adequately to protect this population, and so we need, you

know, and one idea is to just let's take the worst fish off the market to get the largest--because it's not all tuna, it's probably not all shark, it's the large ones, it's the ones that are really that are older that have lived a long time. They are probably also the breeders.

So, you need to figure out how you are going to manage this, and one way to manage it is the size of the fish that is allowed for commercial consumption, and if you had smaller versions of that--I would urge people on this committee to go back and look at the original 1991 NAS study, because they actually went through and analyzed if you reduced the size of the fish available for commercial consumption, what kind of impact that might have.

DR. MILLER: Other questions?

MR. SCHOLZ: Could you maybe just spend a minute, that you had mentioned in passing, a little bit on labels and signage at retail, what would your expectations be considering what you just said about which fish should be made available based on size, what if we have acceptable levels, and because we are targeting a certain part of the population at retail, what would the expectation be to try and address it with either warning label or signage?

MS. SMITH DeWAAL: Well, I think the most effective tool is to use a label that actually affixes to the package, and the reason being that sometimes the person

who is doing the shopping is not, in fact, the at-risk person.

So, if you have it actually affixed to the package as it goes to the home, I think that is preferable to in-store signage, but it still doesn't deal with how to deal with the problem in restaurants. A lot of this fish is sold through restaurants.

You know, it is a very popular menu item, and I suggested actually to the National Fisheries Institute that they run a campaign talking about how it's okay to have swordfish for your 50th, your golden anniversary, but it's not okay to celebrate the birth of your grandchild.

You know, they are trying to put a message out there that people within a certain age group, women within a certain age group should not be eating these species of fish and trying to get that message out because a lot of it, even packaged stuff, label affixed to the package won't address the complete problem.

Consumer education also is limited. I mean we have a lot of messages we need to get out to consumers. Right now I am working on like cook your hamburgers, which after years and years, 10 years of major problems, we are still having to get that message out, and we are still having a limited effectiveness.

So, I just want to tell you from someone who really works hard to get good consumer messages out to the public, and with a readership of 800,000, this is tough to get messages out and have them listened to.

DR. APOSHIAN: I have learned more about fish during the last three weeks than I thought I would ever know in my whole life, but I am a skeptic and I went looking for data, and it is my understanding that the FDA does not have enough money to assay fish for mercury.

So, I took that on myself. I didn't do it in my own lab. I bought 11 cans of tuna fish. I went to the store and I was quite shocked. My wife doesn't let me into grocery stores because she knows I am going to buy cakes and jelly doughnuts all the time, but I was surprised to find there are 21 different kinds of end brands of canned tuna fish, 6-ounce cans. I am not talking about the big one.

I wonder about some uneducated person walking in. But anyway, we took 1 of 11. We bought 11 different cans for I think it was about $12.00.

I called the Clarkson Laboratory. I didn't want to bias this with my own laboratory doing the work. The Clarkson Lab at the University of Rochester is considered to be the best analytical laboratory for mercury in the world. Some people might argue that, but I think the

majority of people would say that, and they were very gracious.

They agreed to analyze the tuna fish. Now, the action level of the FDA is 1 part per million, as I understand it, so I was curious to see how many of these samples were anywhere near 1 part per million.

I also was surprised to find in my reading that something like 27 percent of the seafood consumed in the United States is canned tuna. I think there is a figure something like that, that you can verify by going to some FDA data.

To make a long story short, one of the samples, I won't say the brand name, but it was a sample of low sodium, so if your wife is pregnant, has high blood pressure, I am not a clinician, but I assume someone might say if you are going to eat canned tuna fish, take the low sodium one.

That sample had 1.24 parts per million. It has 207.6 micrograms of methylmercury we are talking about in the six-ounce can. The mean of all these 11 was on the order of 0.233 parts per million.

I am sort of surprised that our government doesn't give the FDA enough money to do this kind of survey. We just did 11 cans, but certainly I would not, and my wife still could become pregnant, that is, I

certainly would not want her to be eating tuna fish with a 1.24 parts per million of methylmercury, and I think something has to be done about protecting pregnant women and, more important for the future of the country, the children that are going to be born to these women from methylmercury, and if we don't advise them by putting it on a can, then, I think we are sort of wasting our time if it is canned.

Certainly, when I go to a store now, or even when I buy a candy bar, I read how many calories are on the candy bar, and what else is in there, and I should think that the labeling of the amount of methylmercury, I know it is difficult in fresh fish bought in the market or in the restaurant, but in the can, the labeling of methylmercury in a can of fish ought to be a relatively easy thing to do.

Thank you.

DR. MILLER: That is an issue. Rather than get into a debate on solutions before we are ready for that debate, that issue will come up when we meet on Wednesday.

Are there other comments?

If not, thank you. You can run off to your chopped meat now.

It is time for a break. Please be back and we will start exactly at 3:10.

[Break.]

Before Dr. Heimbach makes his presentation, Ms. DeRoever has a comment to make.

MS. DeROEVER: This morning I believe I mentioned that we have asked our guest speakers to fill out a form related to possible financial associations with the seafood industry. I believe I this morning I mentioned that one of the gentlemen did, but at this time, the other form has come back and, for the record, I do want to announce that both Dr. Heimbach and Mr. Clewell do have a financial relationship with the seafood industry.

DR. MILLER: The next speakers are Dr. James Heimbach and Mr. Harvey Clewell from the Environ Corporation talking about Fish Consumption Data and Risk Assessment Calculations.

Fish Consumption Data and Risk Assessment Calculations

Dr. James Heimbach

DR. HEIMBACH: Thank you very much, Dr. Miller.

My name is Jim Heimbach. I was asked to just real quickly fill in who is Jim Heimbach. I worked for the Food and Drug Administration for 10 years, from 1978 to 1988, which is a period just about concurrent with Dr. Miller's tenure as the director of the Center for Food Safety and Applied Nutrition.

After that, I spent four years in the Department of Agriculture as Associate Administrator of the Human

Nutrition Information Service, Acting Administrator for two years. That is the part of USDA that does the food consumption surveys, so I had a fairly heavy hand in redesigning the continuing survey of food intakes for individuals to the form that it has taken and the data that we are going to be looking at today.

In 1992, I left and went into consulting, and was most recently with Environ, which is how I am listed in the program, although in point of fact, about three weeks ago, I took early retirement and am now a private consultant. So, I should announce that most of the work that I am going to be reporting here was done while I was at Environ even though I am now presenting this as a private consultant.

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From where I am standing, I can't see this, so I am going to pull this out just to make sure I don't lose my place. You do have a handout version of my presentation. The handout version includes an abstract, which I am not putting on the screen for obvious reasons. It has lots of little words and you wouldn't be able to read it on the screen.

Does exposure matter? Why am I talking about exposure? The EWG brochure suggested that the amount of fish that women eat should not have no impact on whether they receive sound advice about safe consumption levels.

What I am simply pointing out is that the beginning of safety evaluation is looking at exposure, and while I am not going to presume to advise either the Food and Drug Administration or this committee on how you should approach your risk management responsibilities, I am going to suggest that an understanding of what the actual exposure situation looks like is an important starting point in determining how you want to move ahead.

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I so want to start with a very frequently misquoted line from Hippocrates, "Make a habit of two things - to help, or at least do no harm."

Can we move quickly through these slides.

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This is simply a reminder to everyone that fish is not simply a carrier for methylmercury or a carrier for dioxin or a carrier for PCBs or whatever we may be concerned about at the moment.

It is a food. It is a food that is a very important part of the healthy diet.

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It has various benefits.

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Other speakers are going to be talking in far more detail as was already mentioned by Penny Kris-Etherton

earlier. Both the American Heart Association and the American Dietetic Association, representing also the dieticians of Canada, have been recommending actually increasing consumption of fish in this country.

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That being said, let's take a look at what is the real information about fish consumption in the United States and exposure to methylmercury from this consumption.

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For some of you, this is going to be taking you back to kindergarten, but for those of you who do not make a career of dietary assessment, I just want to explain that the standard model that is used by virtually everyone who does dietary assessment as a portion of a risk analysis is that exposure is a function for each source of the food, what is the concentration of the contaminant of concern, and how much of that food do people eat.

You multiply those two together, sum it over all of the different foods, and that gives you the total exposure.

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The information that we are using here or that we are going to be talking about here to estimate exposure are two sets of food consumption surveys. There is the Continuing Survey of Food Intakes by Individuals, known in

typical governmentalese as the CSFII, 1989 to 1991, which was a three-day survey with one day of 24-hour recall followed by two days of food records kept by the respondents. That reports all foods consumed either at home or away from home, and includes estimates of the portion sizes of the food.

In that survey, among the women age 15 to 44, 30.5 percent reported consuming fish at least one time over the three-day period.

A more recent survey is the CSFII, 1994 and 96. This is also a national sample. This has two non-consecutive days of 24-hour recalls. That was part of the redesign that I was responsible for back when I was the Acting Administrator.

Again, though, it reports all foods consumed both at home and away from home, and includes estimates of portion sizes.

In that survey, 25.4 percent of the women age 15 to 44, who provided two days of data, reported consuming fish on at least one of those days.

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Now, here is basically the way we estimate exposure. Suppose we are interested in looking at exposure to caffeine. We might for a fairly typical woman that on day 1, she reports 180 grams of coffee and 240 grams of

tea, and I provided here some representative values for what the caffeine concentration might be in the coffee and the tea, which would lead to estimates of 90 milligrams of caffeine and 72 milligrams of caffeine from the coffee and tea respectively.

On day 2, this woman might have had the same amount of coffee, and on that day she didn't have tea, but she had 360 grams of a soft drink with a caffeine content.

So, what we would simply do is add up the caffeine intake across the 2 days and get 288 milligrams. Since that represents caffeine intake over 2 days, we divide by 2 to get an intake estimate of 144 milligrams of caffeine per day.

Now, for a frequently consumed food or nutrient or contaminant, that is one, that has a non-zero exposure almost every day, this can be up to a point regarded as an estimate of the usual intake.

In other words, it would not be unrealistic to say that this woman, this fictitious woman, usual intake is 144 milligrams of caffeine a day. You might legitimately estimate that her consumption over a week is about 7 times that, and over a month, is about 30 times that.

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However, if you are dealing with an infrequently consumed food, you can't use exactly that model, and my

favorite example of an infrequently consumed food is liver. In the 1994 and 96 survey, about 1 percent of the respondents reported consuming liver.

The 2-day average mean daily intake is 38 grams for these people who consumed liver. That would work out to a little over 30 pounds of liver a year. It would be really not very valid to assume that this 38 grams a day represents a usual intake, that liver consumers consume 38 grams of liver day-in, day-out, over a year.

The 95th percentile would be over 100 pounds of liver in a year. So, we cannot for an infrequently consumed food, just take the information from a 2- or 3-day survey and directly regard it as the usual intake.

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Now, that may sound like something that no one would do, but in point of fact, it does happen, and here is a case where it did happen. This 60,000 newborns annually at risk has become sort of an urban legend. As a matter of fact, we just heard it in the previous presentation.

This was given in the NAS report, the Toxicological Effects of Methylmercury. In the report itself, there was no explanation provided of where that number came from, and consequently, Joseph Levitt, the Director of CFSAN, wrote a letter to Dr. Robert Goyer, the

chair of the committee, asking if he could provide more information about the basis for that number.

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From the letter that Dr. Goyer wrote back on December 6, 2000, this information was provided both in the body of the letter and in an attachment of a table from EPA, that the U.S. population of women of that age is 60 million, 30.5 percent are fish consumption, gives you 18 million. The highest 5 percent consuming 100 grams of fish per day gives you 918,000. Then you apply the birth rate, and you get 60,000 newborns at risk.

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I want to focus on two of these numbers, the percent reporting fish consumption, 30.5 percent, and the highest 5 percent exposed consume 100 grams of fish per day.

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At the top, it just repeats those numbers. The bottom shows where those numbers come from. They were both buried in the EPA Mercury Study Report to Congress from 1997, which reported in the text, it actually wasn't in any tables, that 30.5 percent of women aged 15 to 44 report fish consumption during the 3-day survey period.

This is not the percentage of women who consumed fish, which is more like 80-some percent. This is how many women consumed food during that 3-day period.

Similarly, the 95th percentile fish consumption of women age--it said 15 to 45, I don't know if they changed the base or just wrote the number down wrong--is 113 grams based on the average of 3, 24-hour dietary recalls. Now, it is actually one dietary recall and 2-day records, but the point is that is a 3-day average. That is not for an infrequently consumed food, such as fish, a legitimate estimator of the usual intake.

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In conclusion, the figure on fish consumption is 3-day average. It represents only the distribution of fish consumption over those 3 days by the women who reported fish consumption during that period.

It overestimates the usual intake of fish even for those women who were going to be obviously over-representing frequent fish consumers, and it clearly overestimates the usual intake of fish for the women population aged 15 to 44 in the U.S. The actual best estimator is more on the range of 45 grams, as we will see later.

So, this shows the importance to my mind of doing your exposure estimations correctly.

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When we are looking at an infrequently consumed food, then, we have to have a different way of approaching what constitutes the consumption, and the way that is universally used by FDA, by EPA, by JCFA, part of WHO, pretty universally around the world is to redefine the consumption as being the amount consumed per eating occasion or the portion for short, times the frequency of eating occasions.

So, now, our exposure estimator is what is the concentration of contaminant X in the food, what is the portion size chosen of that food, and what is the frequency with which that food is eaten. You multiply those three together and sum it over all of the sources, and that is your estimator of usual exposure.

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Now, in a dream world, we would have all this information on the same people. The only way we could have that is to have many days of intake data, have data for a month, say, or possibly to have intake data and a food frequency questionnaire administered to the same population, which is now what has been instituted with NHANES, but had not been done before the 1999-2000 survey.

Even there, there are some questions about the validity of food frequency questionnaires.

If you do not have information from the same people, then, what you do is you use probabilistic methods to put these distributions together. So, we will select from a frequency distribution that has a distribution of how frequently women of age 15 to 44 consume fish.

We will select for each eating occasion from what amounts of fish they consume on each of their eating occasions, and we will select from distribution depending on what species of fish we have here from the mercury concentration distribution for that species of fish, and bring these all together with Monte Carlo.

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So, we need information on the concentrations, the distribution of concentrations of methylmercury in all species of fish for which consumption is reported in the surveys. We need to know the fish dishes and the portion sizes that are selected by women age 15 to 44, and the frequency of fish eating occasions.

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First, methylmercury concentrations. There are lots of datasets. This has been alluded to with methylmercury concentration. We specifically and very deliberately use the mean methylmercury concentrations that EPA used in its 1997 Report to Congress.

The reason for this is simply that with different estimation methods, you end up with slightly different numbers. It is nice to have at least some things in common, so that you can understand what is the effect of your methods versus what is the effect of different databases that you used, so we deliberately start with the same data.

We use that same information in a report that we provided to FDA in 2000 and in a paper that we presented at the Society for Risk Analysis in Seattle in December of 2001. Those were only point estimates.

The distribution data came from the National Marine Fisheries Service 1975 Interim Report. The complete dataset that relates to those means has been lost, and despite a lot of efforts by FDA and the National Marine Fisheries and us and the National Fisheries Institute, and who else defined it, we never could, so we found this interim report, and we used that as the basis to use regressions to derive log-linear models of the methylmercury distribution for fish.

I should mention, by the way, that when you use a mathematical model, you realize they are unbounded, whereas, biological distributions usually are bounded, so we actually produced some mathematical estimators of mercury concentration in fish that probably would never be

met with in real life, even higher than even numbers that have ever appeared in analytical testing. We used them anyway.

Finally, when you apply these methylmercury concentrations that were measured on raw fish to fish as consumed, you have to take into account the fact that when fish is prepared, usually with heating methods of one sort or another, it drives off moisture, and since the methylmercury is not driven off, the fish, as consumed, has a higher concentration of methylmercury than the raw fish did. So, that needs to be taken into account when you are estimating exposure also.

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For portion sizes, we used data from the CSFII 94-96, where the foods are reported "as consumed." Now that means that somebody says I had a tuna casserole or I had fish sticks. They don't say I had 13.6 grams of salmon, for example. To go from the food as consumed to how much fish people consumed, we used these two translation files, first, the EPA translation file followed by the recipe files from USDA.

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Here is an example. Here actually are two examples, I am just going to mention the top one, Food Code 28355260 is lobster gumbo. That is a moist heat processing

meaning that whatever is the concentration that we draw in the Monte Carlo for the mercury concentration of the lobster, we will multiply that by 1.14 to estimate what the mercury concentration is going to be in the lobster as consumed in this.

This recipe file shows the lobster constitutes 11.06 percent of this dish, so for every 100 grams of lobster gumbo somebody consumes, the assumption is they got 11.06 grams of lobster.

The second one there is simply to point out that some foods actually contain more than one type of fish, and if so, we need to sum the mercury concentration from all of the fish to estimate what the person is getting from that eating occasion.

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In the CSFII, 593 women reported a total of 717 fish-eating occasions, representing 34 species of fish. Now, this 34 species, there are actually more forms than that because we have fresh tuna, for example, separately from canned tuna. We have fresh lobster separately from canned lobster, and like that. We have farm trout separately from caught trout.

This, you are going to see the significance of in a minute. For the women who reported more than a single fish-eating occasion, the same species was reported 30

percent of the time. This refers back to something that a couple of previous speakers have alluded to, that there is a certain degree of species loyalty, if you will. Women who eat canned tuna tend to re-eat canned tuna. Women who eat salmon tend to re-eat salmon, men, too, I suppose, but we are looking at women here, so you will see what we did with that in a moment.

Also, you will see what you did with this in a moment, 64 percent of the reported fish-eating occasions at home, 36 percent away from home.

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Now, to estimate frequency, first, we used a single food frequency question from NHANES III that asked the number of times fish was eaten per day, per week, or per month. The problem with that data set is it provides very weak information at the higher frequencies of distribution.

One of the things that you have in your packet of materials is an analysis that we provided to FDA back in 2000 on consumption of canned tuna. There, we did a little convergent validity study looking at three different ways of estimating frequency.

One was just using the NHANES question alone. The second brought in the NET survey, which I will describe in a moment. Using the NET survey, actually, it gave us

the highest estimates of frequency of consumption, so it is a very conservative way to go, but it does give us a better estimator, and that is our goal, was to get the best estimate we can.

The National Eating Trends Survey is a diary of foods eaten over 14 days. It is a demographically balanced sample, but it is a national probability sample. They do not report portion size data, they merely report the fact of eating.

We put together four years of data to get a reasonable sample size, and we had a sample size of 3,881 women age 18 to 44 was the closest we could get to our 15 to 44 group that we were using, of whom just over half reported eating fish consumption at least once over the 14 days. Of those, just over half reported eating it exactly once.

However, that is only fish eaten at home. So, first, we multiplied by 30/14ths to estimate times per month and then we estimated total consumption by multiplying by 100/64, remember that 64 percent of fish was eaten at home, to get include meals away from home.

Now, that does mean that the minimum that could be reported, if a woman reported eating one fish meal in that 14-day survey, it would be estimate of three fish meals a month would result from that estimate.

So, then we used the NHANES data to estimate the proportion of people eating fish once or two times a month, and for the analysis we did, of course, we simply did not include at all women who did not report eating fish ever.

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Now, the first study we did with using this approach was done following exactly that methodology except we did not get into the mercury concentrations, we simply used the point estimate from the EPA Report to Congress, and this is what we used for the report that we provided to FDA in November of 2000 and presented at the Society for Risk Analysis.

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According to that analysis, the data on the consumption of fish--and the reason I am going back here is because on the current analysis, we focused only on mercury, and actually, we didn't estimate fish, the Monte Carlo took us right through fish to mercury--estimated that the mean, and I am going to go straight to the mean intake of fish per eating occasion, so that is the average portion size is 32.4 grams.

I want to interrupt to point out that is 2.6 ounces, and there seems to be a tendency to take FDA's advisory of not go over about 12 ounces a week to two, 6-

ounce servings. Very few women eat a serving of fish anywhere near 6 ounces.

It is no accident that the reference amount commonly consumed for the purpose of labeling set by FDA was 55 grams for canned fish and 85 grams for fish steaks and fish fillets, and so forth, and those numbers are actually based on information from the 1989 to 1991 CSFII, about what portion sizes are most commonly chosen.

So, this 72.4 grams that we have represents an average of the roughly 30-odd percent that was canned fish combined with the others. So, the women actually only average 2.6 ounces per eating occasion of fish.

The average frequency of eating fish is about 4.6 times a month, a little over once per week, and consequently, the usual intake is about 11.3 grams a day, which is the equivalent of about 2.8 ounces of fish per week. So, that is the mean fish intake of women age 15 to 44 in the United States.

The 95th percentile intake, taking us up near the top of the distribution, comes out to about 11.3 ounces per week. Now, interestingly enough, FDA also estimated usual intake at relatively high levels of intake using a somewhat different methodology and estimated that the 96th percentile is the 12 ounces of week that is the limit of their recommended intake, so there is very high

correspondence between our estimate of the 95th percentile is 11.3 ounces, and FDA's estimate that the 96th percentile is 12 ounces.

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So, for the current analysis, we did a 100,000 iterations. The basic approach is first you do draw from the frequency distribution. You might draw this woman, has 3 fish-eating occasions per month.

Then, you go into the CSFII dish/portion distribution, randomly select one of the 717 eating occasions, say this is what that woman ate, and then for that portion, depending on what species, how it is prepared, you draw from the methylmercury concentration distribution for that species, adjust for the cooking factor to increase the methylmercury content, and then you go back to the basically draw the second occasion.

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Now, let's see what we did with the repeat meal probability. For the repeat meal probability, based on the fact that women have a preference here to go back to the same foods, what we did was establish a 0.3 probability that when we go back for the second draw for the same woman, for the one that we have drawn, let's say she is going to have fish 3 times in the month.

If our first draw was, let's say, 85 grams of salmon, for the second draw, instead of drawing randomly, if that 0.3 probability comes up, we give her 85 grams of salmon again. Now, we redraw from the methylmercury distribution because it is going to be a new source of salmon, but she has a 0.3 probability of getting exactly the same species and the same portion size again.

This tends to increase for this brand loyalty. Some who was first selected as having canned tuna, is more likely on the next draw to get canned tuna again than somebody who had a different species, and so forth.

What this does tend to do, it tends to draw out your extremes. It increases the 95th, 99th, and so forth, percentiles. It doesn't change the mean, but it puts the percentiles further out because the women who have a preference for relatively high methylmercury-containing fish, will get up higher by repeating that fish for them over and over than if we were randomly selecting the fish each time.

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Here is where we come out. The mean intake of methylmercury is about 1.4 mcg/day. Now, in comparing that with the EPA RfD, which is 0.1 mcg/kg, our intake of course is per person, not per kilogram. For a 60-kg woman, that works out to 6 mcg a day. That is a little conservative.

More often you use 65 kg, which would give you 6.5 mcg a day, but looking at what would be protective for even a somewhat smaller than average woman.

All the way down at the 95th percentile of intake, we are still looking at an intake of about 4.7 mcg/person/day or, for a 60-gram woman, 0.08 mcg/kg/body weight. It is not until we get up well beyond the 95th percentile that we pass the RfD.

At the 99th percentile of intake, we are looking at 8.9 mcg/day. Keep in mind what I told you, though, that this is an unbounded distribution. As we get up high enough, we begin to see more and more the effects of us not drawing a limit on biological plausibility for how much mercury one sample of fish might be assumed to have.

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We compared the intake distribution with three endpoints that have been discussed - the EPA RfD of 0.1 mcg/kg, the ATSDR minimal risk level of 0.3 mcg/kg/body weight/day, and EPA's BMDL of 1.0 mcg/kg/day.

Now, I am not a toxicologist, I am not going to attempt to discuss what the biological significance of exceeding those numbers is. I am simply using those as markers.

What we get is that about 2.9 percent of women, assuming 60 kg women, are above the RfD, 0.2 percent above

the MRL, and something on the order of 0.0001 percent above the benchmark dose.

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Now, you may remember that FDA's advisory had put some emphasis on variety. I highlighted it a couple of places here by putting it in red. As long as you select a variety of other kinds of fish, you can safely enjoy eating them. Just pick a variety of different species.

Now, we can look at the effect of increasing the variety of fish by taking out that repeat meal probability. Remember, we basically made a woman who selected one type of fish for her first meal, to have a 0.3 probability of getting that same fish assigned to her willy-nilly. Just by taking that down to zero, so that each meal is assumed to select according to marker probability, now, canned tuna still has about a 29 percent chance of being selected and porgy has a very small chance of being selected, but we are not enforcing it.

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The effect of dropping that repeat meal probability from 0.3 to zero is to reduce the number of exposures over the RfD by about 10 percent, from 2.9 to 2.6 percent, drop exposures over the MRL by about 50 percent, from 0.2 percent to about 0.1 percent, and exposures over the BMDL were essentially at zero anyway, and they add

another couple of decimal points before the first figure when you increase the variety.

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So, what do we conclude? First, at current levels of fish consumption, women age 15 to 44 are very rarely exposed to methylmercury from commercial fish, and I do want to emphasize we are only looking at commercial fish here. We are not taking into account recreational or subsistence fisher information, which are not fish that are regulated by FDA, and it is not directly influenced by FDA advisory.

They simply are not exposed to levels of methylmercury that would place the newborn children at risk.

Second, FDA's current advisory, assuming it is adequately publicized, is adequately protective of pregnant women, not just average women, but also women who are fairly heavy consumers of fish.

Finally, further, FDA's advice to choose a variety of fish is appropriate advice, it is well-conceived advice, it is certainly very sound nutritional advice, and also is advice that will result, to the extent that it is followed, in reducing methylmercury intake for the same level of consumption of fish.

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Additional conclusions. The exposure data do not suggest a need to revise the current FDA advisory. They do not suggest a need to advise women to avoid or limit consumptions of species of fish other than those listed.

As I said, the modeling indicates that increasing the variety may reduce exposure to methylmercury, and suggests that perhaps that part of the advisory might be strengthened.

Thank you very much for your attention.

DR. MILLER: Thank you.

Comments or questions?

Questions of Clarification

DR. NORDGREN: How many people eat porgy? That's the worst tasting stuff.

DR. HEIMBACH: I suspect very few. That is actually why I selected it as an example of one that is infrequently reported. To tell you the truth, I don't know if we even had a single eating occasion of it reported.

I should mention, by the way, that we are writing up these data now for publication, believing fairly strongly that something is not really a scientifically justifiable piece of material until it has been peer reviewed and published.

DR. SHANNON: If I have been following the afternoon, your data are very different from the data from

NHANES, which suggested that some significant percentage of women have excess amounts of mercury in their blood from a source that seems to be fish, and that there is a fairly good correlation between their fish consumption and their blood mercury.

Can you kind of help me reconcile what you just told us with what she said? They are different, aren't they?

DR. HEIMBACH: Only to a point can I help you reconcile, and actually Harvey is going to address that more. I have no expertise whatsoever in the pharmacokinetics of mercury transport and the linkage between what fish goes in and what ends up in your blood or in your hair is not where I have expertise.

I would simply point out that although for most people, my understanding is fish is the major, not to say the predominant, source of methylmercury in the diet, it is certainly not the only source of either methylmercury or mercury in general.

As a matter of fact, although I have not looked at the raw data, I am given to understand that the woman that was mentioned as having the highest blood level that they got in the survey, 29--was it micrograms per liter--is actually somebody who had reported no fish consumption, so there are other possible sources of mercury in the diet.

So, I would not necessarily expect to find an exact--I would expect to find a correlation certainly, but not necessarily an exact one-to-one correspondence between fish consumption or even methylmercury consumption and blood methylmercury level.

DR. SHANNON: But I am looking at a result based on someone's real data on real American women, and really what seems to be a lot of probability really and more theory on your part, and I see differences, and actually what you just said doesn't help me in terms of understanding why you can say that you don't think there is excess exposure, no reason to change anything when we have real live data measurements in blood to suggest that there is a problem.

DR. HEIMBACH: As I said, I am going to let Harvey address most of this. I don't see that what you see as a difference is that great. I will point out I mean we are talking real live people in the exposure estimate, too, but we are talking about dietary intake, not blood mercury levels.

According to the dietary intake data, we would have approximately 2.9 percent of women ingesting methylmercury from fish above the RfD, and I believe the NHANES had an estimate of 7.8 percent above the RfD based on blood levels.

I would be perfectly happy to suggest that as estimates of this kind of thing go with the unanswered question, those are actually not tremendously divergent numbers.

DR. MILLER: Before we go ahead, I hadn't realized that Mr. Clewell was going to speak also on the subject. Why don't we let him provide his information. That may help clarify some of these issues.

Mr. Harvey Clewell

MR. CLEWELL: I am going to continue on from where Jim left off.

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He was predicting intakes. We use very similar methods in terms of the Monte Carlo analysis, selecting fish meals, to what he described, but we used a pharmacokinetic model to predict blood levels as opposed to just predicting intakes.

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First of all, I was asked to look at the Environmental Working Group pamphlet that is called "Brain Food," that talked about analysis of maternal blood levels, and see if we could reproduce their calculations and what we would say about those calculations.

I will tell you a little about that, and then I will talk about one of the kind of implicit assumptions in

many of the analyses that have been done and talked about, which is the appropriateness of using the reference dose as a bright line for evaluation of safety.

Then, I will give you our analysis, which is the end-gestation blood levels associated with current fish ingestion patterns in U.S. women of child-bearing age.

Finally, I will compare that with the NHANES analysis in terms of a reality check for the calculations.

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The initial scenarios that we ran were based on, as I mentioned, analyses performed by the Environmental Working Group. One was a maximal ingestion of a variety of fish, two, 6-ounce meals each and every week through pregnancy, and then the second was the repeated ingestion of just a single type of fish through pregnancy.

We tried as best as we could to reproduce the assumptions of the Environmental Working Group analysis in terms of the scenario for the exposure, and what we were really doing was using our published physiologically-based pharmacokinetic model of methylmercury kinetics during pregnancy instead of the one compartment model of Allen Stern that was used by the Environmental Working Group.

The model that I am going to show you on the next couple of slides is the same model that Dr. DeRosa mentioned this morning. I did some calculations that were

used by ATSDR in the development of their minimal risk level, and that analysis has been published in that Clewell, et al. 1999 risk analysis.

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This is the model, and there is a lot of compartments, and actually, years ago when I started working on methylmercury, I thought it was kind of funny to suggest using more than one compartment for methylmercury kinetics, but I found when you are doing Monte Carlo analysis, you actually need all those compartments, and in particular, if you are trying to model gestation, pregnancy and gestation, they are absolutely critical to look at the changes in tissues during gestation, changes in fluids.

The mother's tissues, of course, change relative volume at the same time that the fetus is growing, and so all of these many compartments are actually required in order to track the behavior of methylmercury during pregnancy and gestation as opposed to just in a non-pregnant adult.

So, the model actually has time-dependent values for all of the parameters for the various tissues, blood flows, and so on, in both the mother and the fetus.

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You see here just an example of using the model. We actually developed the model originally in monkey data

and then we extrapolated to the human and validated it with the human data. This is a study by Gunderson, which shows the time course. The actual bars there are the best estimates and error bars for the data that was collected by Gunderson for a 50 mcg/kg/day methylmercury exposure in the diet of monkeys, and the dotted line represents conception.

You can see a fairly complex time course of methylmercury even though the daily dose is constant, and this is because, of course, the change in the tissues in both the fetus and the mother through pregnancy and also the mother's tendency to change her dietary ingestion rate, the number of kilograms she ingests per day of food.

So, the solid lines then, they are thick because actually, the model is dosing each day with whatever the dietary intake is, and so there is a little bit of increase at the time of the meal, but those are the predictions of the model for this monkey study, the lower points and line being the mother, and the upper one being the blood of the infant at birth.

I want to mention while this reminds me regarding sensitive window. If you have high enough mercury levels, you can actually kill the fetus. See the fetal toxic levels, that will occur in the first trimester, they won't make it past the first trimester.

Lower levels, still very high, Minamata type levels, you actually will survive and be born, however, there will be severe malformations. Choi [ph] has shown that those primarily occur. The major malformations, primarily the effects occur in the second trimester.

For the subtle neurological effects that we are talking about now, the group at Rochester has argued, and I agree, that the effects are primarily third trimester and probably continue on postnatally if there were exposure. Typically, mercury exposures reduce at birth because you don't immediately begin eating fish, and there is not very much lactational transfer.

So, the susceptible window for what we are worrying about here is the third trimester.

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This is an example one of the validation datasets. This is a mother-infant pair from the Iraqi poisoning. Amin-Zaki recorded the blood levels and hair levels of this individual. She was admitted because of toxicity to the hospital after she had already been pregnant for some time.

They were able to reconstruct her exposure using hair segments, and so you can see the circles and the solid line are the observed and predicted maternal hair levels during the period of pregnancy as shown by the solid bar

near the bottom there, that goes from about 200 days to 460 days.

Then, once she was admitted, they began to measure her blood, and those are the triangles. You can see the model predictions for the blood. It shows the concentrations during pregnancy were actually much higher than they were during early pregnancy, were actually much higher than they were at the time she was admitted to the hospital, which was during the third trimester.

Finally, when the infant was born, then, they measured its blood levels. Those are shown as the diamonds, and you can see that the model also predicts the blood levels at birth. So, this is the model that we used in this analysis.

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Unfortunately, we were unable to reproduce the Environmental Working Group's results for their first scenario. The 12 ounces per week, we were able to generate a lot of different numbers, but none that were anywhere near the ones that they had reported in their figure, so we finally gave up.

We were, however, able to reproduce the second scenario, which is using a single type of fish. It was a simpler analysis, and it was easier for us to figure out what they had done.

So, when we used the same pharmacokinetic model they used, the Stern model, then, we were able to reproduce their data, but as I will show you on the next slide, if we used the model I just showed you, we actually get lower blood level estimates.

I actually anticipated this would be true because in some earlier work I did, I found that Allen Stern's model overestimates blood concentrations resulting from dietary methylmercury exposures. He was doing a Monte Carlo analysis, and wasn't actually validating the model against the exposure data that was available, so it just happened that the model parameters give you high estimates.

That is documented in a publication, which is an entire of issue of Toxicology and Industrial Health, Shipp et al--I am one of the al's--that came out recently.

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On the left is the actual figure from the Brain Food pamphlet. We have made all of the curves black except for the ones that we reproduced or attempted to reproduce. We just selected some in order to test whether our understanding of the methodology was correct.

If you compare the green and purple and yellow and orange lines, you will see we got fairly good reproductions given the fact that we were using a very different pharmacokinetic model. The only one we weren't

able to really reproduce was sea bass, which is the highest value up there, but so we felt reasonably good that we probably understood what the Environmental Working Group was doing.

We were using the Stern model there, I am sorry, but so we were able to roughly reproduce what they had done.

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Now, this slide shows the difference between using the Stern pharmacokinetic one-compartment model and using our model on the right. You can see that the sea bass now is the purple line in the center of the diagram on the right. All of the predicted concentrations come down.

I don't actually know how to describe what these plots are. I presume you will hear that from the Environmental Working Group. The Y axis is kind of astounding. Percent increase in the number of women whose blood mercury level would exceed 5.8 parts per billion for more than a month of pregnancy. I have never actually seen a risk metric described that way.

At any rate, it is sort of a measure of blood levels, and I believe that the EWG's are overestimates.

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This has been described in three different talks this morning, but I just want to remind you that the basis

of the reference dose, the RfD was the neurological effects in fishing, the populations that were exposed for generations.

The dose-response was used to predict a benchmark dose. I am a benchmark dose modeler and a BMR of 5 percent is quite conservative. Actually, in studies where they have compared it with the NOAEL, it is more conservative than a No Effect Level, so this is a very conservative estimate of an effect level. This is not an estimate that should be comparable to a lowest observed adverse effect level. It is actually more conservative than a no observed adverse effect level.

The Boston Naming Test, BMDL of 5 was used with an uncertainty factor of 10 to drive the RfD.

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As has been mentioned a number of times, the Faroe Islands study was a large study, but it was compromised in terms of implications of fish ingestion by the consumption of whale meat, as well, which is not only higher in methylmercury and the blubber contains PCBs, but also it's a seasonal thing, so that there is more spiking in terms of large presentation of mercury to the fetus.

As a result, there is a continuing controversy which will not be resolved regarding co-exposure to PCBs and other potentially confounding factors, such as the

Torshaven effect. Some people with low mercury mostly lived in Torshaven, whereas, the people with high mercury typically live out on the Islands. It is very difficult to work out that kind of an issue.

One quick comment on the PCB co-exposure. I am the only one here who can probably tell you this, because Kenny Crump is not here, he's in China teaching Chinese how to speak English, but he was the one who, at that meeting that Chris DeRosa mentioned, pointed out that if you have co-exposure to two contaminants, and the uncertainty in the measurements of one of those contaminants is greater than the other, then, the statistical analysis will always tend to suggest that the primary factor in the effect was the more precisely defined co-exposure chemical.

So, this is a statistical outcome, and I can't get into the details of it, but that was the basis for that decision by that particular group in North Carolina that it would really be nice if you could have an exposure without PCBs because it is probably not going to be possible to de-convolute the impact of PCBs, the fact that on a particular test, it was not significant for PCB doesn't mean that it doesn't have an effect on the benchmark for mercury, and the extent to which it has an effect is not determinable.

DR. MILLER: Five more minutes, please.

MR. CLEWELL: Okay, good.

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So, it's a highly conservative estimate for continuous exposure throughout pregnancy. The measure that was actually used in the Faroe Islands was the end pregnancy blood level, cord blood level. The blood levels could fluctuate higher or lower than that value for durations during pregnancy, that was not the maximum value achieved during pregnancy and trying to compare it with a maximum value achieved would be inappropriate.

To compare with the RfD blood level, one needs to calculate the end pregnancy blood level to be able to compare apples with apples.

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The Presbyterian Book of Order says that despite the fact that there is but one truth, there will always be matters upon which men of goodwill will nonetheless disagree, and here are some men of goodwill, various organizations, who disagree about the proper limit for methylmercury exposure. At the low end, as they always are, is the USEPA, and they work up from there through ATSDR, FDA, WHO, and TERA has a risk assessment, the Toxicology Excellence for Risk Assessment, Mike Darson's group, has one on their web site, International Toxicology Estimates of Risk 0.35, so you can see there is a range of estimates.

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So, what I did in order to try to characterize for our analysis the results, I used not only the RfD blood concentration, but also the MRL blood concentration, and also the BMDL, which was actually the "No Effect level" in the Faroe Islands study.

You can see this is the distribution, this is our main results. We have determined that 2.3 percent of the women at the end of pregnancy would be at or above the RfD blood concentration of 5.8 mcg/liter and that about 0.4 percent would be above the MRL.

So, this actually compares reasonably closely with Jim's analysis on the basis of intakes. I think he was 2.9.

As a reality check, the question that came up is exactly the question I had, so how does this relate to the data that has been collected?

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We have a NHANES analysis, and you can see that the results of the NHANES analysis, as was mentioned earlier today, I might be off by 0.1 percent there. I can't remember whether she said 7.8 or 7.9, but 7.8 percent of women at or above the RfD blood concentration, and as it turns out, 0.4 percent above the MRL.

So, although there are a small proportion of women that are above the RfD blood concentration at the end of pregnancy using--well, no--well, the drawback of this is this is not women at the end of their pregnancy. This is women. Some of them were pregnant when these NHANES measurements were made, most of them were not.

So, this is women in general, age 14 to 45. So, it is not exactly the same thing that I just showed you, it is not. So, you can't really say, well, this is ground truth and the other thing is just a prediction.

The other thing is predicting what we want to know, which is what you could relate to the RfD blood level. This is something that is similar to that, but different, but it does, in my mind, just as Jim said, that's good agreement to me.

When I say it's about 3 percent, and this says it's 7.8 percent, that is still a small fraction of the population being above the RfD, and complete agreement about the MRL, 0.3 mcg/kg/day level, that only less than 0.4 percent of the women would exceed that. Also, it agrees that none of the women are above the BMDL, the No Effect Level of 58 mcg/liter.

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This is the summary. Maternal blood concentrations may indeed sometimes exceed the RfD blood

concentration for worst-case or high-end exposure scenarios.

The use of the RfD as a bright line for evaluation of safety, though, is not appropriate. That is not the only information one should use in order to process the question of is there a potential for health effects.

As Dr. Grandjean said, they were looking for subtle effects, these are not sick kids. So, the kinds of things that you have to bring into play are all of the various factors that determines the word "safety."

The realistic exposure scenarios result in maximum blood levels that are within a factor of three of the RfD and are well below the effect levels in the Faroe Islands.

Thank you.

DR. MILLER: I just want to remind the committee that the Environmental Working Group will have an opportunity tomorrow to present their data. I want to make sure that we understand that.

Questions of Clarification

DR. APOSHIAN: Can we go back to Dr. Heimbach for a minute? I am a little disturbed about one comment that you made, namely, that there are other sources of methylmercury than fish or seafood.

To my understanding--and you can correct me--

DR. HEIMBACH: What I meant to say, if I didn't say, is there are other sources of mercury, I don't know if they are methyl or not.

DR. APOSHIAN: That is not what you said. You said other sources of methylmercury.

DR. HEIMBACH: I apologize. In the blood mercury, there could be other sources of that.

DR. APOSHIAN: But since you brought up again other sources of mercury, I think the committee ought to realize that there are other sources of mercury, not methylmercury, but other sources of mercury that can also do similar damage to a child and to a pregnant woman, and that is mercury from dental amalgams.

I am not trying to tell you that mercury from dental amalgams is safe or not safe. I am not getting into that argument. All I am saying is it is well established, the World Health Organization has published such data, it is in the peer-reviewed literature that the major source of the American population to mercury is from dental amalgams, whether it is toxic or not, I don't want to get into it.

But the other point I want to make about methylmercury is there is increasing data that methylmercury in the brain is slowly converted to mercuric mercury, as is elemental mercury that gets from dental

amalgams to the brain is slowly converted to mercuric mercury.

So, in the real world, you have got to consider more than one kind of mercury in any kind of risk assessments, and I think Harvey knows that. I am a great admirer of Harvey's, by the way, we have known each other for a long time, but it seems to me that just to make a risk assessment on methylmercury and ignoring the potential of amalgam mercury or elemental mercury affecting the brain is dangerous.

Again, I will say one more thing and then I will shut up I think for the day because I am getting tired, I don't know about the rest of you, but there is a classical example in this country of a family in New Mexico who ate a pig, a swine, that was contaminated with methylmercury, a large amount of methylmercury.

One child was born--the woman was pregnant, and two other young children--anyway, one of those children lived to 21 years of age, and the Rochester group was involved in these analyses also. At 21 years of age, that person who died and had been exposed to methylmercury had a level of inorganic mercury in her brain 100 times the level that is normally seen.

So, I think in the real world, toxicity usually is not due to one compound or one agent. In the real

world, you have got to consider the other sources of mercury, but i did want to clarify the methylmercury.

MR. CLEWELL: I will go ahead and take that as a question, so I can answer something, but I agree with you certainly in terms of risk management particularly, since I have a risk management, we need to consider all the sources. We were just asked to look at the contribution from fish ingestion, and it would be obviously problematic to do an estimate of the contribution from amalgams, because it is very poor data in that area.

Another area that I had learned from ATSDR, to my shock, that contributes to high end exposures is religious practices and putting mercury in candles. So, as Jim mentioned, the highest blood level in this was for someone who said they don't eat fish, so there is something else going on with that woman.

So, this analysis is indeed--and then I wouldn't say that that is all the difference, but that is one of the reasons for the difference between the results of our fish ingestion analysis and the NHANES survey, which the NHANES is looking at total mercury in the blood, so it is amalgams, burning mercury, everything.

DR. MILLER: But surely, you would not disagree with any attempt to reduce any one of the sources.

DR. APOSHIAN: I would be delighted if every one of the sources were reduced.

DR. MILLER: I am glad to get it on the record.

DR. DWYER: I don't know which of you to ask, but if you could go back to the 60,000 estimate again and just give us what your estimate would be.

DR. HEIMBACH: I will answer first. I don't have an estimate, I seriously don't.

MR. CLEWELL: Why did you want to go first?

DR. HEIMBACH: There are a lot of issues that go into a question of, quote, how many newborns are at risk from anything, and I don't know the answer for anything.

All I know is that the basis that was provided to explain where the NAS Methylmercury Committee derived that 60,000 number was not a valid basis for establishing a number of newborns at risk. That is all I know. I do not have an estimator of my own.

MR. CLEWELL: I also don't have a number, but I can tell you a reason for a substantial overestimate, which is because the analysis requires assuming that the uncertainty factor of 10 actually doesn't lower the risk. If the entire population remains at the risk associated with the benchmark analysis of the Faroes population in spite of a reduction of 10-fold, and so if I had to hazard a guess, I would say it is probably 10-fold too high,

because if the high end exposures are in the vicinity of the RfD, which is 10-fold below where there is the MDL 0.5, then, statistically speaking, even if you assume a linear model for the risk, which is the kind of worst-case typically, then you would say that the risks were actually down about 10-fold on a population basis, so much lower is about all I can really say.

DR. RUSSELL: Perhaps, Dr. Heimbach, you can answer this. I was very impressed with Dr. Aposhian's tuna fish data showing the huge variability of levels can to can, and I am wondering, is that known for other fish species, what kind of variability it is?

He was showing over 12 times variability for the same type of canned, chunk, white tuna in water, for example, just a huge variability, and I was wondering what is the variability in other fish species.

I was wondering also, a question I asked before, does it vary by geography of where the fish is caught.

DR. HEIMBACH: I don't have answers to all of that. The answer to the first part is that generally speaking, the methylmercury concentration in fish does seem to be quite highly variable. It certainly has to do with the maturity of the fish, size of the fish.

I would be somewhat surprised if it doesn't have some geographical variability, but I don't know for certain that it does.

I was surprised at his numbers simply because that--I am not surprised at the average he found, the 0.22, that's probably in about the right range. FDA's estimate based on several hundred cans analyzed in the early 1990s was 0.17, which is again, as we said, for these kinds of estimates, when you are within 20 percent of so of each other, that constitutes agreement to my mind. The 1.24 is kind of a shock. Certainly, FDA never came up with anything anywhere near that high in its hundreds of analyses.

If there isn't some sort of error in the analysis of this can, I suspect something odd sort of happened that caused a contamination of the fish, I don't know. The variability is not normally that variable, particularly for something like canned tuna, which tends to, by the nature of how the fish is processed, have less variability can to can than you would have fish to fish for raw fish, but it does tend to be fairly highly variable concentration.

DR. MILLER: Dr. Hotchkiss.

DR. HOTCHKISS: I am just trying to get a picture I understand of some of these numbers. When you are talking about 2.3 percent above the reference dose, you are

considering EPA's reference dose. Earlier, there was a number of 2.9 percent, I don't think that is a lot different, but am I understanding that correctly?

MR. CLEWELL: 2.3 percent was based on blood level calculations at end of pregnancy, and 2.9 percent was based on just tissue changes.

DR. HOTCHKISS: Diet. So, we are faced with a number that was about 7.8 percent based on the HANES data for which you are saying that basically, at least in a dietary sense, some important considerations were not accounted for, particularly for a food that is eaten infrequently, is that right?

DR. HEIMBACH: No, no, I am not saying that. I am saying my estimate based on fish intake alone was about 2.9 percent above the RfD. Harvey's estimate, based on both fish ingestion and pharmacokinetics, is that we would expect about 2.3 percent blood levels above. Now, I was strictly talking ingestion. Then, the HANES number that we are talking about, the 7.8 percent, is the total mercury concentrations in blood that are above, and what we are suggesting is that some of that total mercury in blood for some individuals may be due to sources other than fish consumption, and that might explain why the 7.8 percent, there is a few more above the RfD in actual total mercury

content that would be predicted based on fish ingestion alone.

DR. HOTCHKISS: So, if we took that over the population, we just divided roughly that half of the population is female, which it is a number smaller than that--

MR. CLEWELL: Sixty million.

DR. HOTCHKISS: So, if we multiply 2.3 percent times 60 million, we are still talking about roughly 3 million women who, on the lowest estimate, are above the reference, EPA's reference dose. At the high end, we are talking at something like 10 million.

So, we are considering that whatever end of this data you believe, you believe the lowest end that we have heard so far, we are talking roughly 3 million women in that cohort or group, up to something like 10 million.

MR. CLEWELL: I am not very comfortable with back-of-the-envelope calculations, particularly when you can get 7 percent of 60 million being 10 million. I don't think that works.

It might be better if you actually let somebody calculate it. I would guess that it is actually less than that, but as I just got through mentioning, that is assuming that the risk at the reference dose is the same as the risk at the benchmark, which is 10-fold higher. In

other words, that uncertainty factor didn't buy you anything in terms of protecting health.

So, it is actually not a good calculation. You know, sometimes it is better off not doing a calculation that is meaningless than it is to do one and then people will believe it.

DR. HOTCHKISS: Let me understand that then. The lowest we have heard is 2.3 percent, what you are suggesting is 2.3 percent receive above the RfD dose from fish, and you are saying that that population is 60 million, but you are telling me I can't multiply--

MR. CLEWELL: So, that is 1.2 million people that are above the reference dose, that's right.

DR. HOTCHKISS: So, the low end is 1.2 million, the high end of what we have heard, somewhere between--

DR. HEIMBACH: What I would like to say, and I said at the beginning I am not going to presume to advise either FDA or this committee how to do your risk management, but I do want to put this in the context, however, and I will let somebody from FDA or from EPA address this also, in estimating what are safe levels of intake of contaminants, pesticide residues, food additives, and so forth, there is never an expectation that you are going to have 100 percent of the population with expected exposures below level of safety.

FDA standard rule, and there are other people here who can address this, for intake of food additives, color additives, GRAS ingredients, is look at the 90th percentile of intake, and assure that the 90th percentile of intake is within safe levels. EPA's approach to dealing with pesticide residues historically has been to look at the 95th percentile level of intake, and assure that the 95th percentile of intake is within safe limits.

Now, all I am saying is that is the rubric that has most often been used. I am neither recommending it, nor disagreeing with it.

DR. HOTCHKISS: Thank you. Let me follow that up. Thank you for that clarification. I, too, am a former FDA employee and understand what they are doing there. What I am trying to get is, okay, let's take whatever number you like. If you take the 90th percentile, how many actual individuals is that, and I think that is something we have to consider.

DR. MILLER: Dr. Nordgren.

DR. NORDGREN: You had a study from 1975 on levels of methylmercury in fish. You threw that up. My question is, are those levels different than what have in our book here from 1998?

DR. HEIMBACH: I have not done a comparison of them. I used those data sources because those are the data

source that EPA used for the 1997 Report to Congress on mercury exposure.

MR. CLEWELL: I might say that our analysis actually used all the data, not just the '75 study, but used everything that is out there, and we ended up in roughly the same place. I don't think there is any evidence that the levels have changed.

DR. MILLER: Dr. Shannon.

DR. SHANNON: Would it be fair, then, I guess this question goes to both of you, to summarize your main findings as being the rate of exposure to excess mercury in women is much less than NHANES would suggest, the reference dose that is being used is useless, the mercury measured in NHANES may not be from fish at all, and we don't have anything to do here, because there is no reason to make any changes?

MR. CLEWELL: It sound a bit argumentative to me. I might be being defensive, though. I thought we were actually just trying to project what we would expect the blood levels to be for methylmercury exposure from fish ingestion, and you can kind of take your own spin on it, which I am sure you will.

I wasn't asked to give a risk management input, so I won't. You have the data in front of you. You can interpret NHANES any way you want to. We were just trying

to--I was actually pleased, really, that the prediction of the distribution of blood levels for women eating the reported fish ingestion is consistent with NHANES. I think it probably is actually to some extent you could argue that it is a better estimate of the contribution of fish ingestion, but as Vas has mentioned, from a risk management perspective, it is all important exposure to mercury.

One of the things I find unfortunate is that the agencies don't do a very good job of translating their exposure limits into health and safety guidance, and that people will take a dose-response analysis in a study of an affected population, divide it by an uncertainty factor, and then talk as if the value they just derived is the borderline between safety and some sort of developmental deficit, which I think unfairly scares the population.

DR. MILLER: We have reached I think the last part of our day's work. It is part of these hearings that at the end of the day, we provide some period of time for what is called Public Comment. Groups, and so on, who want to make short statements, are allowed to make them at that time if they have signed up with the Secretary.

We have three requests for today. First, Dr. Rhona Applebaum of the NFPA.

Rhona, you have five minutes. Remember, it is the end of the day.

DR. APPLEBAUM: Absolutely, Dr. Miller. Trust me, I won't go beyond my five minutes. Our written comments are at the desk, so I won't belabor the entire testimony before you today.

Thank you for this opportunity and NFPA appreciates our time here to offer our comments on FDA's Consumer Advisory on Methylmercury and Fish Consumption. NFPA supports the use of sound scientific information in decisions affecting food safety and the food industry. Most importantly, we strongly advocate the use of sound science as the basis for any and all health advice given to consumers.

There is every indication that FDA made its decision on how to frame the fish consumption advisory to consumers on the basis of the best science available to them.

Advice to consumers on fish consumption, as with all health advice--and we heard this, this morning, as well as this afternoon--is a very complex issue that cannot and should not be addressed by looking at any one piece of information.

We believe FDA met the challenge of integrating information from a wide variety of sources on the numerous factors that must be considered in providing sound,

actionable advice to the public on safely consuming fish, which has repeatedly been recognized as contributing to a healthful diet.

FDA, from our perspective, and that of recognized scientific experts and groups, looked at the totality of the evidence and the data before them, including quantities consumed and the benefits of fish consumption.

As a public health agency, FDA then made a risk management decision and produced a risk communication message that provided the facts to consumers, as well as the necessary advice on methylmercury and fish consumption.

Consequently, it is inconceivable that any public health agency, particularly FDA, would risk consumer health by doing anything other than looking at this issue from an objective scientific perspective.

Health officials, the scientific community, and consumer advocates all meet regularly with the regulatory agencies. In fact, during the process of revising its seafood consumption advisory with respect to methylmercury, FDA actively sought input from, and met with, a number of different stakeholders to ensure that all sides of this issue were heard and valid scientific information considered. We believe this exchange of information is appropriate and necessary for bringing the best available science to bear on any action.

NFPA itself regularly meets with regulatory agencies overseeing U.S. food production, and we provide them with information on industry programs and activities affecting safe food production, as well as with research findings that are intended to assist their science-based decisionmaking. In turn, the food industry regularly seeks information and input from the regulatory agencies on a variety of food science and food safety issues.

NFPA does not always agree with the Agency's conclusions or decisions on all matters. In fact, Dr. Miller, that would take more than five minutes for me to identify all those areas. However, we firmly believe that FDA bases its decisions on what they believe the facts to be after careful and diligent efforts to identify, assess, consider, and interpret relevant, scientifically valid information. Their goal is always the health of the public, all subsets, all sectors.

In closing, let me state again my Association's belief that FDA did an exemplary job in the development, focus, and wording of the Advisory with the information available to them at the time on the risks of methylmercury in fish and the documented benefits of fish consumption with focus on the targeted population, that being pregnant women and women of child-bearing age.

Again, we thank you for this opportunity to provide our comments on this very important topic.

Thank you.

DR. MILLER: Thank you.

The next speaker is Dr. Lee from the National Center for Policy Research. Five minutes, please.

DR. LEE: Good afternoon. I am Dr. J. Huang Lee. I am a physician and the senior medical policy analyst at the National Center for Policy Research for Women and Families.

I would like to thank the committee and the speakers today for a day of very interesting presentations.

It appears that the Food and Drug Administration's current efforts at protecting the American public from the health risks of methylmercury are inadequate. First, the Agency is unable to provide consumers with truly up-to-date information since the Agency has failed to adequately monitor methylmercury levels in commercial fish supplies.

Second, the FDA's rationale in performing its advisories is flawed and poorly suited to the chronic long-term nature of the health risks associated with methylmercury contamination.

Third, the FDA has failed to effectively disseminate its findings and recommendations to the general

public. Most consumers remain unaware of the health risks associated with methylmercury in fish, and even the most health conscious members of American society tend to be poorly informed of the dangers.

During a Consumer Roundtable meeting with Director Joseph Levitt and other senior officials from the Center for Food Safety and Applied Nutrition here in College Park on June 20th of this year, I asked whether the Center was monitoring levels of methylmercury in commercial fish supplies. To my dismay, I was informed that the Center was not currently monitoring methylmercury levels and had no plans to initiate a surveillance program.

We heard very briefly mention of possible budgetary reasons for this, but as a scientific explanation for the Center's disinterest in a surveillance program, I was informed by the Director of the Center's Office of Science that methylmercury levels in fish do not change significantly over time.

I am puzzled as to how this can be known with any certainty if no one is monitoring methylmercury levels in the commercial fish supply. Historical data are no substitute for diligent surveillance.

One can imagine how numerous factors including changing levels of environmental mercury contaminants from fossil fuel, utility plants can alter the level of

methylmercury contamination if both freshwater and saltwater fish.

In order to provide the American consumer with valid and up-to-date information, the Center should initiate routine surveillance of methylmercury levels in all commercially available fish species.

In addition, commercially processed fish products should be monitored for methylmercury contamination in a manner analogous to the monitoring for bacterial contamination.

I should note that with the previous discussion regarding methylmercury levels in canned tuna, the range in 248 samples of canned tuna ranged from non-detectable to 0.75 parts per million, so the range offered here today is not that surprising.

To continue, even if we were to assume that reliable and valid information is available on methylmercury levels in fish, the FDA has not properly used these data in formulating its consumer advisories.

Currently, only those fish species with the highest known levels of methylmercury are named in the FDA's consumer advisory. This approach may be suitable if the main concern were acute methylmercury toxicity, however, in the United States, the primary threat for methylmercury is chronic long-term exposure.

It is therefore crucial to formulate advisories based on the overall public health impact of a particular fish species. The question is which fish species and fish preparations will contribute most to methylmercury exposure in vulnerable segments of the population.

Answering this question requires one to consider the annual per capita consumption of a particular fish species in addition to the mean methylmercury levels, and this is seen in the Seychelles Island study.

For example, canned tuna accounted for 75 percent of the canned fish consumed in the United States in 2000. In that year, more than 980 million pounds of canned tuna were supplied to the American consumer.

Although methylmercury levels in canned tuna are thought to be lower than in other fish species, and lower than that in fresh or frozen tuna, the sheer quantity consumed makes the public health impact of canned tuna far greater than that of any other species.

It is more likely that women and children will be exposed to methylmercury through canned tuna consumption than through eating shark, swordfish, king mackerel, or tilefish.

Therefore, canned tuna should specifically be named in any future advisory on methylmercury. Consumer advisories are a step in the right direction, but they are

inadequate for disseminating information about the health risks associated with methylmercury contamination.

It is fair to say that most Americans remain unaware of the current advisory for shark, swordfish, king mackerel, and tilefish. Even fewer are aware of the FDA's recommendation to limit fish consumption to an average of 12 ounces of cooked fish each week.

The occasional advisory news story is simply not enough to properly inform the American consumer. So, what should be done?

We can begin by placing the advisories where consumers are most likely to see them, on the packaging of fish. If the FDA believes pregnant women and young children should limit their consumption of cooked store-bought fish to an average of 12 ounces a week, why not say so on the package?

DR. MILLER: Dr. Lee, can you consider summing up?

DR. LEE: Yes, I am almost finished.

If the FDA believes that canned tuna consumption should be limited to an average of 9 ounces per week, why not place such an advisory directly on the cans?

In summary, clearly, the FDA must do better in collecting reliable and valid information regarding methylmercury contamination in fish. It is time for the

Agency to adopt a more public health oriented approach to formulating its advisories.

More importantly, the American consumer deserves better access to the information issued by the FDA. I urge the Advisory Committee to recommend significant changes in the way the Agency is managing this serious problem.

Thank you.

DR. MILLER: Thank you.

The next and final speaker is Dr. Richard Fisher. Five minutes, Dr. Fisher.

DR. FISHER: Thanks.

I want to thank the panel for allowing me a few minutes of your time.

My name is Rich Fisher. I am a dentist. I have practiced in suburban Washington for the last 30 years. The first 10 years of my practice I, like most of my colleagues, placed mercury-containing fillings into my patients' mouths thinking I was doing them the best service that I knew how.

In 1981, it was first published in the dental literature that the mercury from dental fillings escaped the fillings and was absorbed into the human body. We didn't know back then what we know now as far as how much was absorbed and to what levels they accumulated, but it seemed to me, as a health practitioner, whose first mission

is to protect the health of my patients, that I would not use amalgam mercury fillings after that period of time, so in 1982, when I learned of this research, I stopped using mercury fillings, so for the last 20 years I have been doing it right, so to speak.

I am a member of the American Dental Association although I am not here as their official representative, as you might guess. Dental amalgam or mercury fillings contribute, as Dr. Aposhian mentioned earlier, more mercury to the human body burden than all other sources put together by far.

The data that we have from World Health Organization, from Dr. Aposhian's study, as well as from the textbook published by Dr. Clarkson and Dr. Freiberg over 10 years ago, all show the same thing, and that about four times the amount of mercury that we absorb and retain from diet is coming in from our fillings, so we are getting four times that we are discussing here today.

I am here to applaud your efforts on the dietary sources of mercury, but I do think we need to make some efforts to your colleagues within the FDA to address the even bigger aspect of this problem.

To put it in another way, one average size dental mercury filling contains a half a gram of mercury. That,

according to EPA standards for human exposure for adults, would exceed 100 years' worth of exposure.

From another perspective, if we were to disperse that half a gram of mercury into a 10-acre lake, you wouldn't be able to eat any of the fish coming out of that lake.

There has been move afoot in this country to get rid of amalgam, to phase it out. There is a bill before Congress now to do that. I would love to see the FDA support that action. Other countries, such as Canada, Sweden, Norway, Denmark, United Kingdom, and France have already issued advisories in those countries to avoid using mercury fillings in pregnant women and young children, which again are the most vulnerable citizens.

Looking at the data that we have from those studies, I have calculated for the nine-month gestation period, that dietary sources alone contribute about 620 micrograms into the pregnant woman during the nine-month gestation.

About 10 percent of that goes into the fetus or about 62 micrograms enters the fetus from the mother's diet during that nine months. During that same nine months, the calculations for the mercury going into the mother from her fillings, on average, run 2,700 micrograms, and again, 10 percent of that, which is 270 micrograms, goes into the

fetus, again, four times the amount that the dietary exposure generates.

In addition, there is a secondary route of exposure coming from dental offices, which is largely overlooked. There have been several studies now, the last of which was funded by the American Dental Association, that shows that between 14 percent and 75 percent of the mercury coming out of municipal wastewaters is traced back to dental offices from the scrap amalgam, the stuff that is not put into the tooth, that is left over and disposed of.

This, of course, gets bioconverted in the aquatic and marine environments. It is converted into methylmercury, which then gets into the food chain and the tuna, and so forth. So, I think this is another part that dentistry has to clean up its act.

So, again, I am here for two reasons today, one, to applaud your efforts in what you are doing here, and I appreciate that very much, and to plead that you lobby your colleagues within the FDA to look at this other aspect of mercury poisoning, which is the dental amalgam issue.

Thanks very much for your time.

DR. MILLER: Thank you.

This brings us to the end of this rather long day. We will adjourn for the moment until tomorrow morning at 8:30, when we will begin promptly on time I hope.

[Whereupon the proceedings were recessed at 4:30 p.m., to reconvene on Wednesday, July 24, 2002, at 8:30 a.m.]

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