at

ATDEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR FOOD SAFETY AND NUTRITION

FOOD ADVISORY MEETING

METHYLMERCURY

Thursday, July 25, 2002

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at

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P R O C E E D I N G S

Call to Order

DR. MILLER: It is very important today, particularly because so many of our colleagues have to make their flights this afternoon, for us to stick to the agenda as closely as possible and, if at all possible, to try to save time as much as we can.

I will say a few words later on about how we can approach the development of recommendations. I indicated to you yesterday one approach, and I hope you all thought about the remarks that you might want to make, thought last night about the remarks you were going to want to make. But, even there, we are going to have to apply a great deal of discipline if we are going to get through these things.

Several of the questions are interrelated and they don't necessarily have to be answered all independently. I have a suggestion about how we might approach this again when we come to it on the agenda.

The first speakers this morning are from the Center for Food Safety and Applied Nutrition, Mr. Lou Carson and Dr. Marjorie Davidson, who will talk about an overview of consumer advisories and focus groups.

Overview of Consumer Advisories and Focus Groups

DR. CARSON: Good morning.

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I am the first of actually four speakers from FDA. I just wanted to let you know about that. I am going to speak about the stakeholder outreach that we conducted back in the fall of the Year 2000. Then Dr. Davidson is going to speak on the focus group and education plan rollout for the advisory. Then Dr. Michael Bolger will be discussing the basis for the advisory. Mr. Phil Spiller will then discuss international advisories that exist currently.

[Slide.]

FDA has a long history of informing the public on potential acute and chronic health threats from the food supply, so methylmercury is not our only endeavor in this regard.

[Slide.]

I think as you have been listening over the last few days, it seems that all of this information is new. I wanted you to realize that, basically, we have gone through a very similar process in the fall of 2000. The issues before us then were we had an existing consumer advisory that was issued in 1994, 1995. We received and read and analyzed the July 2000 NAS report and we decided, based on the NAS report, we needed to see public comment on the adequacy of our current advisory which was the 1994, 1995 advisory as it relates to the NAS report.

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[Slide.]

What we did, under Mr. Levitt's signature, we sent out a Dear Colleague letter to stakeholders. We sent these invitations out and held a series of public meetings. All of the discussions and invitations were part of your package so you should have already had those.

[Slide.]

We asked the stakeholders, in order to focus our discussions with them, a series of questions the first of which was, given the NAS report and the emission standard set by EPA, should FDA revise its advisory to consumers and, in particular, to vulnerable populations such as pregnant women and women who may become pregnant. If so, what should that advisory say?

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We asked the second question; given the potential nutritional contribution of fish and seafood to a healthful diet, should the consumer advisory be crafted so that it conveys the benefit-risk balance of methylmercury-containing fish; if so, what should that content of such a message say?

Third; with additional Seychelles study data expected to be released next spring, what impact, if any, should such new data have on the timing and content of any FDA advisory.

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Four; what other factors, if any, should impact a decision on whether and how to revise the current--again, that is 1994, 1995--advisory.

Second to last; what methods of communication should FDA use best to convey such an advisory.

Last; how could FDA measure its success in reaching the consumer audience including the vulnerable populations.

[Slide.]

We met with a large number of stakeholders over November, December 2000. These included the National Academy of Sciences, Dr. Jacobson who spoke to you earlier as well as Dr. Goyer and others; industry groups, some of which have presented this week; consumer groups, Dr. Zuckerman and Caroline Smith DeWaal and others; health professionals, the Pediatric Society and others; the Seychelles group. Dr. Clarkson visited with us during that time.

We also held a fifty-state call to get interest and input from all of the states who have advisories. We met several times with the Environmental Protection Agency and we also held a conference call with Canada, our largest trading partner, on how they were dealing with this issue.

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What was some of the feedback that we got? Again, in your package, you have all of the notes from each one of those meetings that we held. Generally, there was a lot of disagreement. Generally, people did not agree on when and how to proceed.

Again, remember, at the time we conducted these meetings, the Seychelles report was to issue in the spring and that loomed large in many people's thoughts and discussions at that time. Oftentimes, what we heard was advice that was contradictory or certainly in conflict.

We also heard that the Faroes, the Seychelles and the NAS points of view were all expressed and espoused as the correct scientific basis. As you have heard this week, it is fairly consistent with that. What people did agree with was that we needed a simple consistent government message and they stressed that emphatically. They also stressed that diet and health were certainly important women's health issues.

So, in December 2000 to January 2001, we convened and looked at all of comments made by each one of the stakeholder groups. We also had, during that time, Congressional inquiries and letters instructing us one way or the other. Again, those Congressional inquiries were often in conflict. They were not of a consistent voice.

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We held an EPA consultation to discuss our approach in arriving at our decision.

[Slide.]

In January 2001, again as we did, in consultation with EPA, FDA and EPA concurrently, our methylmercury consumer advisories, I believe we did adhere to the agreement from the stakeholders. While it has been of much discussion here this week, I believe we did come out with a simple message and that simple message is avoid four fish, shark, swordfish, tilefish and king mackerel, and choose a variety of other fish.

That was the simple message we arrived at.

[Slide.]

The FDA and EPA advisories are linked. You also heard from Dr. Southerland how we have coordinated our outreach efforts. Whether one or other of us are at meetings, we are sharing those outreach efforts. But, also, I wanted to bring up the state perspectives. We have also linked and show the state advisories through our website. As the State of Wisconsin and State of Alaska mentioned this week, they are important partners in getting the message out.

Certainly, we use state and local public-health officials to be multipliers in getting our message out to those targeted populations.

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[Slide.]

In the January time frame, while we have heard comments that people do not believe that FDA has been very successful in getting our message out, we heard, loud and clear from the State of Alaska, that our message was reaching their population and it was causing them great confusion.

As Dr. Middaugh presented to you earlier this week, and as FDA has reported in its data tables, the residue levels of methylmercury in fish in Alaska are very, very low. We, in our message in discussing how much other variety of fish people should eat, 12 ounces per week, was causing somewhat of a hardship and, certainly, a confusion factor in Alaska.

So, FDA, in consultation with Alaska, came up with the language.

[Slide.]

Again, Dr. Middaugh mentioned this language earlier in the week but I will just refresh your memories. We did say, and we did add to the existing advisory. We did not change it otherwise. We simply added a paragraph. "Some kinds of fish are known to have much lower than average levels of methylmercury and can be safely eaten more frequently in larger amounts. Contact your federal, state or local health departments or other appropriate

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food-safety authority for specific consumption recommendations about fish caught or sold in your local areas."

[Slide.]

In March 2000, we revised and reissued the advisory containing that paragraph and it is here on our website. We also, in that issuance, put on our rationale document, the basis for that advisory, as well as the data tables of data that FDA had at that time for all the fish that we have tested for methylmercury.

With that, I will conclude. I will turn it over to, now, Dr. Davidson to talk about the focus groups and our education program.

DR. MILLER: We will hold the questions until both the talks.

DR. DAVIDSON: Thank you, Lou.

[Slide.]

As mentioned, I am here to provide a brief overview of the focus group research that went on as the scientists deliberated the content of our advisory. These focus groups were held to examine the communication style and format an advisory might take.

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The most important purpose of the advisory was, of course, to minimize the risks of methylmercury to the

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unborn child of pregnant women as well as women planning to become pregnant. We wanted to present this information in a manner that was understandable as well as motivating to women so that they would adopt the advice we recommended.

At the same time, we were also aware of the benefits of eating seafood and we didn't want women to lose the benefits of doing so.

[Slide.]

Twelve focus groups were held during October and November 2000 in three locations; Calverton, Maryland, Denver, Colorado and Cambridge, Massachusetts. The first eight groups were held in Calverton and in Denver and they consisted of four groups at each site; one of young women, most of whom were pregnant; a mixed-gender group with college education; a mixed-gender group with less than a college education; and a mixed-gender group with an unrestricted education background.

The four remaining groups that were held in Cambridge and Calverton consisted, in each city, of one group of young women, some of whom were pregnant, and a mixed-gender of unrestricted education.

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The goals of the focus groups were, first, to examine the various styles and formats that an advisory might take, as I mentioned earlier for presenting the

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information about the risks of methylmercury in fish. We also wanted to gauge the participants' response to this information, how they might act on it.

We hoped to use the information that we gathered to develop recommendations on what combinations of format and advice would work in getting the information out. We tested portions of various existing messages, some state advisories, our former FDA advisory, draft advisories from EPA and others to try out different formats.

[Slide.]

We found out that participants really had very little information about methylmercury. They knew about mercury, itself, and that it was a toxic substance but they didn't know much about methylmercury in fish. We found out that it would be necessary to explain about the risks of methylmercury in fish, why it is a problem and how it gets into fish. Otherwise, since people didn't know anything about it, they would just simply dismiss our message.

Here you can see how we dealt with this information need in the advisory, that mercury falls from air into surface water, that bacteria transform mercury into methylmercury and that fish absorb methylmercury from water as they feed on aquatic organisms.

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We also found that it was important to distinguish why some fish have higher levels of mercury than others. If there wasn't any explanation about this, then the participant groups, particularly the pregnant women, thought all fish were a risk. Here, again, you can see in the advisory how we dealt with this issue; "nearly all fish contain trace amounts of methylmercury which are not harmful to humans. However, longer-lived, larger fish that feed on other fish accumulate the highest levels of methylmercury and pose the greatest risk to people who eat them regularly."

[Slide.]

Participants consider this message about the dangers to pregnant women as very important. There was no skepticism about the message at all. Highly alarming informational material wasn't necessary nor particularly useful. Just a simple, factual message was all that was necessary to convince pregnant women to adopt the advice.

This, again, is how we dealt with that; "Methylmercury can harm an unborn child's developing nervous system if eaten regularly." This was sufficient.

I would like to point out that there was a spillover effect about any warning about the risks of methylmercury. Many participants from the general group, those who weren't pregnant, frequently felt that if fish

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held risks for pregnant women that there might be problems with it for them, too.

[Slide.]

As the focus groups proceeded, the effectiveness of different forms of advice was analyzed. An example; we used presentation of long lists of fish in different groups and people were asked to pick certain amounts of fish from one group and certain amounts of fish from another.

It was quickly apparent that the participants were confused by that. They said they were. They said it was too complicated and they also demonstrated that they couldn't effectively use that kind of information. They wanted the information kept simple and pregnant women, in particular, wanted to know just what fish is good for them to eat and what they shouldn't be eating.

We subsequently refined our messages and tested them favorably in that regard.

[Slide.]

If a message was presented to the groups to limit consumption of a certain species of fish, it was often received as a message not to eat that species at all. For example, we tested our former advisory, FDA's former advisory, about limiting the consumption of swordfish and shark to once a month and it was typically read as do not eat that fish at all.

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[Slide.]

Our advice to limit the amount of fish you at generally, however--this is as opposed to limiting the amount of a certain species--was not viewed as particularly alarming by participants. Here, you can see the final advisory information that we used. "You can safely eat 12 ounces per week of cooked fish. You can choose shellfish, canned fish, smaller ocean fish or farm-raised fish. Just pick a variety of different species."

I thought it was interesting yesterday when the gentleman from Wisconsin handed out their advisory. They had an interesting way of presenting it on the first line where they talk about the weekly consumption levels, 6 ounces to 12 ounces of fish. Then, of course, they had their monthly recommendation and the "do not eat" one on the line below that.

[Slide.]

What about tuna? At the time the focus groups were conducted, the issue of whether the agency would distinguish between different forms of tuna hadn't been decided, that is tuna filets versus canned tuna. It was apparent, however, from the focus-group research that if the agency wanted to do this, it would be a difficult communication to achieve.

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Of course, FDA's advisory only concerns commercial fish. As mentioned before, FDA collaborated extensively with EPA during the whole advisory development process. At the time FDA's new advisory was announced, EPA simultaneously released theirs as well for fish caught in fresh-water lakes and streams.

The advice is, "For pregnant women and women of childbearing age is to eat fish once a week from fresh-water lakes and streams and check with your state or local health authorities for any advisories in your area." EPA also added the caveat that if you are following FDA's advice to eat 12 ounces of fish, then you shouldn't eat any fresh-water fish.

[Slide.]

We have heard a lot in the last couple of days about women who have been eating fish seven times a week or three times a day and we know we have got a hard road ahead of us to get the word out to people so that they will adapt our twice-a-week advice. So we have extensive communication outreach activities under way.

Our research, as well as the research of many of other people, finds that most people get their health education through the media, so we have worked that avenue quite hard. We have reached all daily and weekly newspapers with information about methylmercury. We have

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also distributed special outreach efforts to print electronic media outlets that reach women in particular, like women's cable channels, women's shows. Magazines such as Family Circle, Good Housekeeping, Parenting Magazine among others, have had articles on methylmercury in them and have helped us reach millions of women.

We have also reached over fifty health-professional organizations as well as exhibited at many of their conventions with this information as well as 3500 local health departments. We also collaborated with EPA in mailing to gynecologists and obstetricians throughout the country this information about methylmercury.

Authors of books on pregnancy and child-rearing were also reached with information. Membership associations that reach women have been sent information, like the PTAs. Grocery stores have been contacted. I actually was pleased--last month, I picked up a fish food-safety-advice pamphlet at the grocery store and there was information on our methylmercury advisory in it.

We have also sent out special targeted information to special audiences like through the National Indian Health Board. We have done advertising through radio UNICA to Spanish-speaking audiences as well as participated in health fairs reaching them. We have also sent information to all the WIC directors throughout the

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out that reach low-income pregnant women and we are also working on a special effort with our local public-affairs specialist and local health departments to reach high fish-eating populations, to work on formulating messages that will work better with these groups.

I do want to take this opportunity to stress, however, that a fundamental rule of health education is you have to repeat the message often in many different places and many different ways and that we will be continuing to do this.

[Slide.]

In conclusion, I will add that we will evaluate our outreach efforts through our FDA consumer survey. This is a national survey of consumer attitudes, knowledge and behaviors. We use this to measure trends. We were out in the field this summer collecting data so this will help provide a baseline of information where we can compare our success or our failure in getting the message across in the months and years ahead.

Thank you.

DR. MILLER: Thank you.

Questions of Clarification

DR. MILLER: Comments or questions? Dr. Shannon?

DR. SHANNON: Over the last couple of days, we have heard opinions and even some evidence that as many as

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30 to 50 percent of women don't know this message. Do you find that number believable and, if so, what is going wrong in terms of outreach and education?

DR. DAVIDSON: I find that number very believable at this point. Since the advisory was released, we have just begun our efforts to reach people with information and we are just finally getting the trickle-down effect, for example, the brochure I mentioned. Another pregnant woman just got one in her information, a methylmercury advisory in her guide to pregnancy.

There is a delay in getting information to the people who publish these materials who enter and get them out to the information distributors. As I mentioned, it isn't a one-shot process. It has to be said over and over and over again in many different ways. So I would expect that that will change over time.

DR. LEE: Hi. Ken Lee. I think, Dr. Carson, you mentioned that you consulted or conferred with Canada, but I am also wondering, do you have any perspective on what the regulatory status of this methylmercury is in Japan? Did anyone look into that?

MR. CARSON: Later on, Mr. Phil Spiller is going to be talking about international advisories. Perhaps, he can address that. I don't personally have Japan. And Dr. Bolger will also talk about that.

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DR. BOLGER: Do you want to know what their action level is in Japan?

DR. LEE: What are they doing about methylmercury in Japan? Are they tracking it?

DR. BOLGER: In terms of the kinds of biomarker studies?

DR. LEE: Are they measuring methylmercury in their fish? Are they measuring it in their people?

DR. BOLGER: They have done a fair amount of work in terms of analyzing levels of fish. That has been fairly well done. In terms of in population studies, it is a little more problematic. They have a particular problem in Minamata and there is as lot of data that has been generated recently. The problem with Minamata was happened back then. So there is a fairly ongoing effort.

DR. LEE: With all that data in Japan, is there any hope of using that to help establish a "no-effect" level in the United States?

DR. BOLGER: You are going back to Minamata.

DR. LEE: No.

DR. BOLGER: Just using the population study and epidemiology studies?

DR. LEE: I am looking at a population that consumes a fair number of predatory fish.

DR. BOLGER: And looking at health outcomes.

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DR. LEE: Yes.

DR. BOLGER: I am not aware of any cohort study in Japan. Katie, are you aware of any?

DR. MAHAFFEY: No.

DR. BOLGER: Katie was in Japan not too long ago, so she can.

DR. MAHAFFEY: I am told that the Japanese are doing some additional screening on their population. Their values among men are a good deal higher than in the U.S. I have been told some numbers I think we around an average of 4 or 5 for men.

Women, apparently, consume fish in a somewhat different pattern from the men in Japan. Their hair mercury levels are lower. I don't think there are good data though that give an overall population estimate for Japan that would be similar to, say, the NHANES data that we have.

DR. BOLGER: But I am not aware of any like Faroes or Seychelles type study being done in Japan.

DR. APOSHIAN: I noted with interest the people that you had met with at your stakeholders meetings. I must say I am glad to see that you met with Dr. Thomas Clarkson. He is a friend of mine and I admire him. I also admire Dr. Philippe Grandjean. I notice that there was no one on that list from the Grandjean laboratory or Dr.

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Grandjean. Dr. Grandjean is Professor at Boston University. He is available. I was just wondering why your group did not also have input from Dr. Grandjean who headed the Faroe Island study.

MR. LEVITT: I think I am the right person to answer that. We began with a meeting with the Academy. Because the Academy had relied on the Faroes study for their recommendations and had not relied on the Seychelles study, we thought it was worth talking to the Seychelles investigator to get their perspective on it. That is why we did it that way.

As you see, when we set up this meeting, we invited both investigators to come. But that is how it unfolded.

DR. APOSHIAN: Thank you.

DR. FISCHER: It was said in the first presentation that the EPA messages and the FDA messages were linked. I think probably that link means a computer link. But, in fact, I think the EPA messages and the FDA messages, in order to be effective, need to be consistent as much as possible.

So I am wondering when you are talking to the stakeholders, if you are going to get them to get them to understand and appreciate your message, it should be as much as possible the same as the EPA messages and other

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messages that they are getting. Otherwise, they are not going to take them in, I think, or believe them.

So I am asking how well, how consistent are these messages that are appearing in the media, in magazines, and so on that you talked about. Are they consistent or do they, in fact, show inconsistencies that are harmful?

MR. CARSON: I will try and, perhaps Marjorie will also. I believe, to the extent possible, these messages are consistent. Again, FDA has authority over commercial seafood and EPA has authority and technical assistance for recreational seafood.

If you look at the messages both are putting forward, both are saying avoid, in our case, the four major fish. Then we are both saying choose a variety of fish. The difference really comes down to the amount of choosing for a weekly portion and that is directly relational to either recreational fish or commercial seafood.

Other than that, I think the messages are quite consistent. We do recognize, and it was pointed out by the State of Wisconsin yesterday, the State of Alaska, that we are trying to put forward as complete a message as possible. We do believe they are consistent. We believe our message a well as EPA's is consistent with the National Academy of Science.

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We believe if you do follow the message, avoid the four fish, choose a variety, you will be in that safe zone.

DR. MILLER: Dr. Hotchkiss?

DR. HOTCHKISS: Joe Hotchkiss. I have a couple of questions I want to follow up on that last one. Was any consideration given to EPA and FDA providing a joint statement here. I suspect the answer is going to be no because of statutory authority differences but I am not so sure I agree that those statutory authority differences would preclude a joint statement that would cover the waterfront.

MR. CARSON: I think we tried to achieve that in simultaneously issuing our consumer advisory.

DR. HOTCHKISS: My question is not simultaneous. My question is joint.

MR. CARSON: I am not sure if--is your question did we attempt to craft one that was joint?

DR. HOTCHKISS: Yes. If not, why not? In other words, the same statement signed off by both agencies that would cover both commercial product as well as sports-fishery products.

MR. CARSON: Again, it is our authority to cover commercial seafood and it is EPA's authority to cover the other seafood.

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DR. HOTCHKISS: Those differences in authority will preclude a joint statement?

MR. CARSON: I don't know that they would preclude a joint statement but, certainly, EPA, I don't know, would want to sign off on something that is not their authority or would we want to sign off on something that is not our authority. So we certainly have consulted and we try to work as closely with EPA as possible but we did not, obviously, issue a joint statement.

DR. HOTCHKISS: The second question, and maybe you addressed this and I just got it, but I wondered specifically what measures of effectiveness or ineffectiveness of your message do you plan or have in process to gather data on; in other words, a research mode of how effective is our message.

DR. DAVIDSON: As I mentioned, we will be using our consumer trend survey. We have also begun discussions with states that combine the commercial and their local seafood advisories to examine how that is accepted as well.

MR. CARSON: I would also add that we have heard this week the data from the NHANES survey. The NHANES survey that you have been the recipient of is from 1999. So we would hope that the NHANES survey from 1999 and 2000 would serve as a baseline prior to our issuance of the advisory and, over years that we receive those reports, we

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will use that public-health surveillance data to also show if our advisory is having an impact.

DR. MILLER: Mr. Scholz?

MR. SCHOLZ: Brandon Scholz. I have two questions. One, Dr. Shannon, I think, just mentioned that there are some estimates that 30 to 50 percent of the people don't get the message. Do you have goals, or do you have a sense of the penetration of your message? Are you able to say, "By our outreach efforts, we expect to reach X percent of, we believe, the target population?"

Then, I think it is just follow-up question to Mr. Levitt, at what point can you measure the success of penetrating the message?

DR. DAVIDSON: As I said, we will be keeping track of the trends of knowledge as well as behavior on the part of women who are pregnant. We have had really quite a lot of success on the other aspects of food safety that we have done through our educational efforts. We have had as much as 30 and 40 percent changes over a small period of time in consumer knowledge and behavior which is actually quite extraordinary for health education.

Many times, they say as much as 3 percent of change a year is quite an extraordinary amount of change.

MR. SCHOLZ: Did you find out from your focus groups their sense of where they get their best

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information? I notice in the outreach that you have described and as others have described, some traditional avenues related to healthcare and others, but did you get a sense from participants in the focus groups what they thought was the best--where they get their best information?

DR. DAVIDSON: We didn't ask that particular question from these particular focus groups but, in previous ones, we found that pregnant women mostly get their information from their physicians which is why we mailed to all of the physicians in the country the information as well as worked through the associations to get the information out.

The problem, as mentioned the other day, is physicians are very busy people who have a very short time with each patient and often don't get around to discussing that particular item of information.

MR. SCHOLZ: Just one more. I was just curious. You had three focus groups, two on the East Coast and one in the Rocky Mountain States. We saw yesterday, I think, from presentations that a number of states in the Mid West are pretty active in this. Was there any effort to expand either out to the West Coast in the Mid West to focus-group in those states as well or to test in those states as well?

DR. DAVIDSON: No; we didn't.

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DR. APOSHIAN: Dr. Nordgren.

DR. NORDGREN: My question has been answered.

DR. MILLER: Dr. Aposhian?

DR. APOSHIAN: The White House initiated the Raleigh meeting primarily because the FDA, the EPA and the ATSDR, whatever it is called, could not agree on RfD for methylmercury. One of the recommendations of the Raleigh White House conference was that the three agencies involved work together and attempt harmonization.

This was also a recommendation of the National Research Council's methylmercury study. My question is exactly has been done in an attempt to reach the harmonization that the White House and a large group of mercury investigators have urged on the three agencies. Has there been a specific meeting with all three groups to try to solve this problem or is it still just the three groups working independently and occasionally an employee of one group talking to another? What has been done for harmonization?

DR. MILLER: I am not sure they are the two people to answer that question.

DR. BOLGER: I am very aware of the recommendation. In some ways, I think when I go through my presentation, I will capture what you are getting at. But there is also a new White House effort to coordinate the

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agencies in regard to the whole mercury issue. It really stemmed from the Gulf Mercury Mobile meeting.

So there is an ongoing federal effort to have the different agencies coordinate on mercury.

DR. APOSHIAN: Will you tell us what that will be later on during your discussion?

DR. BOLGER: We have only had one meeting. It just started. Where it goes from there, I am not entirely clear. As first meetings go, there was a lot of probing and wandering about the countryside to try to get some focus on what the effort needed to be about.

But part of that, obviously, would have to encompass the issue you have just asked about.

DR. MILLER: Dr. Montville?

DR. MONTVILLE: A good deal of the confusion appears to come from EPA versus FDA and sports fish versus commercial fish. In your focus groups, is that meaningful to consumers? Do they distinguish between commercial fish and sports fish or do they think commercial is in a can and everything else is something else?

DR. DAVIDSON: There is mixed knowledge about that.

DR. MONTVILLE: If it is a distinction that the consumers don't make, then I question why we should be making it in the advisory.

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DR. DAVIDSON: I can appreciate your concern. The focus groups really did understand the message. We described it as fish caught be family and friends as recreational fish, and that helped distinguish.

I do want to point out that both FDA and EPA talk about each other advisories and the information because we work very closely together not to make them separate messages. The announcements may have been simultaneous but the education is cojoined.

DR. MILLER: Last question.

DR. FRIEDMAN: Sarah Friedman. I just wanted to know, in your presentation, you say that you gave a lot of information. You mentioned how you needed to educate the members of the focus groups about what you are talking about, about the kinds of fish, about the mercury, how it gets into the water, how it gets into the fish and so forth. But you will not have a chance to do that with the regular consumer in the short and semi-sweet message.

So I see a certain problem there in the assumption that yes, people need to have further information but then we cannot give it to them because we need to make it very short, concise. Just a comment for your consideration.

DR. DAVIDSON: There is, of course, always the challenge of fitting your message in the marketplace of all

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the other ones, but just those few short terms were sufficient to advise people enough about the risk that they were willing to act on it.

DR. FRIEDMAN: You will have a chance to do that with the advisory? The discrepancy that I see is the interaction with the focus group versus the interaction with the general public.

DR. DAVIDSON: Our information that we send out also has the explanation of mercury and fish in it.

DR. MILLER: Dr. Scherer?

DR. SCHERER: In the first presentation, you talked about the additional language that you added as a result of discussions with the Alaska situation. I was wondering why the decision was made to, in a sense, increase the consumer burden by just making it a very general statement; in other words, see your local conditions.

The concern that I would have is that that increases the likelihood that they won't do anything because, in fact, trying to find who do you ask makes it much more difficult.

DR. DAVIDSON: There is no question that the first advisory is an overall general nationwide advisory. That is why I mentioned that we were working particularly

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with local areas to frame messages specifically targeted to special groups.

DR. MILLER: I am going to have to call this to an end so we can move on, but just two quick comments. I think this is a reflection of the difficulty of providing an actually accurate, totally supportive, message and providing one which is simple which people can understand and read right away. That is the paradox and I don't think this has been resolved in this particular case.

The other issue, I strongly suggest that you consider the possibility of joint information materials with EPA including a joint statement. I don't think there is any legal reason why the two agencies could not issue a statement together. I doubt it. I really would like to know more about that. You would know that, Joe.

There have been other statements before from both agencies and multiple agency statements, so I don't think there is any reason for that not to happen except in terms of confusion.

We are going to move on to Dr. Michael Bolger from CFSAN who is going to talk about the basis for the advisory.

Basis for the Advisory

DR. BOLGER: Good morning. I am going to stand out here because I cannot see the screen behind the podium.

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Before I start, I was asked yesterday to put together a table that basically incorporated several safety standards and different levels of methylmercury in fish and the corresponding level of ingestion. So the top table is in grams and then I was asked to do it in ounces because some people don't think in grams. So that is the bottom table.

I would like to point you to, let me get this right, the bottom table under 0.12 and the reference dose. You will see under there about 12 ounces. That is a very key level of consumption because it is the level of consumption that we identify in our advisory. So I want you to sort of keep that in mind because, across the top, you have 0.1, 0.2, 0.3 up to 1.0. But, right next to 0.1, we have 0.12. That is the average level of methylmercury in the top twenty commercial species which are dominant in the marketplace. They are something like 97, 98 percent of the market.

So just keep those numbers in mind as I go through this. You also have another figure which I think you got yesterday that describes the NHANES data, the graph. I just want to point out that was a draft version because it said 7 percent of women exceed the reference dose. It is 8 percent. Actually, the n at the bottom is a

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smaller n than is in the cohort. I will show you an updated version but, essentially, it is the same curve.

[Slide.]

I have the task, and I have always felt sorry for people who have to give wrap-up presentations and here I am with the unenviable task of trying to wrap up the key points that you have heard over the last two days. You have been hit with a lot of information and so what I am going to try to do is try to capture the key points in all the information we have presented.

I am focused on the science exposure component of the advisory consideration. Marjorie already gave you an overview of the focus group.

[Slide.]

So I am going to start you off with four key conclusions and walk you through. Then I am going to end up with these four key conclusions

Number one, the primary purpose of the FDA's consumer advisory to pregnant women and women of childbearing age is to maximize the protection of fetuses from neurologic harm from methylmercury exposure resulting from the mother's consumption of commercial fish.

In developing the advisory, the FDA believes that when these women follow the advisory, and I will come back to this, the resulting exposure to methylmercury should be

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below every one of the, and I used just a generic term, tolerable level. Call it what you want; reference dose, MRL, TDI, whatever term you would like to call it, as I said the other day, they are different terms for basically the same thing.

Intake levels established for methylmercury including the recommendation of the NAS report and EPA's reference dose which is, as you have heard, the most conservative of all the safe levels that have been identified.

[Slide.]

Number three; according to baseline data, exposure levels to methylmercury, 92 percent of women of childbearing age, and this is the NHANES data, already consume below the reference dose. Thus, they essentially already are eating according to the advisory.

Number four; while the remaining women, approximately the top 8 percentile still have a margin of safety of about eight-fold. That is an average for that upper 8 percentile. FDA's goal is to provide the women with the information to decrease their methylmercury exposure through the advisory. This will be accomplished either through better adherence to the instructions in the advisory or by making appropriate adjustments to the

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advisory consistent with the best scientific information available.

So that is our goal. That is how we are going to try to track the success of the advisory. But I want you to bear in mind that top 7 percent are not just consumers of commercial fish. We can't do this alone. Heavy consumers of fish are also heavy consumers of just freshwater fish so part of that 7 percent, we can impact. Part of it, we cannot. That has to be dealt with particularly by our friends at EPA and at the state level.

[Slide.]

Methylmercury is a potent neurotoxin--no debate there--that can have severe adverse effects in humans at very high doses. You heard that about Minamata, in Iraq. These effects have been seen in poisoning events in Japan and the fungicidal grain in Iraq. That was not a contamination in Iraq. That was seed that was treated with a fungicide.

The problem was that the label instructions were written in English and the resulting contamination occurred because the individuals who used the grain did not understand English. So it was actually an unfortunate misuse of a grain treated with fungicide.

Normally, the primary exposure is via the consumption of fish. Methylmercury is fish. I need to

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emphasize that. There are a few cases where we have had events like the poisoning episode in New Mexico with a family but those are rare events. I mean, methylmercury is fish.

So the central public-health question involves the level of methylmercury exposure through the consumption of fish over time that would be necessary to cause adverse effects in the fetus.

[Slide.]

So, in 1979, FDA established its action level of 1 part per million. This stemmed from the fairly famous or infamous Anderson seafood case involving swordfish. The basis of it relied primarily on the Japanese poisoning events in a study of Swedish fishermen who actually have levels that were not that different from Minamata but were asymptomatic as well as an updated estimate of exposures.

I just want to point out that we originally had a level of 0.5 and, based on these two issues--in other words, that the dose-response data, our consideration initially was deemed to be overly conservative and that our estimates of exposure were deemed to be overly conservative based on this new information that was provided at that time.

Based on the conclusion regarded at the time as being conservative that subtle threshold effects, and this

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is the paresthesia, tingling in the extremities, occurred at an adult hair level of 50 parts per million. This really was based primarily on the Japanese events.

It was not based on the Iraqi event because we did not have the information on the Iraqi event at that time. But, as I said before, the dose-response information out of the Japanese events has always been very problematic and the designation of 50 parts per million was deemed by some as being overly conservative. This was deemed to be a prudent determination.

There were some, and, believe me, this was before my time, who argued that the threshold for the adult response was not 50 but was 150. So I just wanted to give you sort of that background. You hear this number 50 and you get this idea that there was this certitude associated with it. No; there was not. There was still a lot of debate at that time about that level.

Hair mercury levels in the Faroes and the Seychelles are, on average, about 5 parts per million. They are very close when you look at their distribution of hair levels in these two populations.

[Slide.]

According to the NHANES, as you have heard from Dr. Susan Schober, the average hair level is about 0.2 parts per million. Just as a reminder, the average in

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the Seychelles and Faroes was around 5. So the 5 parts per million in these two studies approximates the uppermost percentile of exposure in the U.S. population; in other words, beyond the 90th percentile, particularly when you look at hair. But that is all we have right now for hair. We only have up to the 90th because of the robustness of the dataset available.

The data provided so far by NHANES have not revealed any women of childbearing age whose body burdens exceed the highest no-adverse-effect dosages that have been derived from either the Seychelles and the Faroes. And I will come back to this again.

[Slide.]

So, in summary, severe adverse fetal effects occur in high doses based primarily on the Japanese and Iraqi events. Issue; do these effects occur at low doses consistent with the background fish levels consumed over time in the United States.

The relative exposures are 50 parts per million for the adult response, 5 parts per million average in the two key epidemiological studies and the average from the NHANES of about 0.2.

[Slide.]

So the longstanding question has been whether the developing fetus is more sensitive to methylmercury than

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the adult. When we put forth our action level in 1979, that was the number-one issue we identified as being the outstanding issue that had not been resolved.

Studies of the Japanese poisoning events were not definitive enough. I have already pointed that out, particularly in terms of the fetal response. There was no question that there were kids who were grossly compromised. There is no debate there. The problem was what was the dose that was associated with it, particularly with less obvious symptoms in the children.

There were kids who were grossly compromised. But we are concerned about in terms of fish levels in this country about less subtle neurological responses.

So, as a result, two very large, well-designed studies which you have heard about, Seychelles and Faroes, have been conducted to try to answer this question.

[Slide.]

To date, as you have heard, the Seychelles has reported no adverse effects associated with methylmercury although Gary Myers did report in the information to be published that they did notice--I think there is a decrease in activity in males. But then they have also observed a beneficial response so it is sort of a mixed-bag message.

The Faroes study has reported adverse effects in the fetus at levels of exposure lower than those that cause

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effects in the adult. Both studies, as you have heard, have been the subject of much discussion. In the Seychelles, there has been the power argument. In the Faroes, there has been the confounding effect-modifying role of other environmental contaminants in the diet and the dose-effect relationship.

These have received much discussion and will continue to receive much attention and much discussion.

[Slide.]

So, faced with this ambiguity, the FDA, in the mid-1990s--this is 1994, to be exact--took a prudent course of action by issuing a consumption advisory for the purpose of protecting the fetus. So we issued an advisory in 1994--did they ever see that? No? Okay--based on the possibility that the fetus is more sensitive to methylmercury than the adult.

As you have heard, in 1999, ATSDR came out with their tox profile, derived a minimal risk level of 0.3 micrograms per kilogram of body weight per day based on the no-observed-adverse-effect level in the Seychelles and the use of a 4.5 uncertainty factor.

In July 2000, the National Academy Committee recommended that EPA base its RfD on the Faroes. They didn't actually recommend a reference dose. They walked up to the threshold but didn't actually derive a reference

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dose. I think there is sort of a misconception. I have always heard about the NAS number. There is no NAS number. NAS said, "This is what you ought to do. Here is the study to rely on. Here is the uncertainty factor you need to consider." And they stopped there.

[Slide.]

So, in summary, we have, in terms of increased fetal sensitivity, in Japan and Iraq, we have suggestive but no definitive information on fetal responses. In the Seychelles, so far, the gist of what is coming out of the Seychelles is no adverse fetal effects. The Faroes reported adverse effects, as you have heard.

FDA issued its advisory based on this possibility. This was its first advisory in 1994. ATSDR, as Chris DeRosa pointed out, assumes sensitivity but relies on the Seychelles. NAS recommended Faroes which EPA then followed their recommendation.

[Slide.]

So, in response to the NAS committee report, FDA revisited its advisory and made it more conservative in several ways. It now recommends abstention, total abstention of four species. We increased the number of species that we had originally advised. Originally it was swordfish and shark. We then put tilefish and kingfish into the abstention message.

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It now includes a recommendation on the total consumption of fish on a weekly basis as the 12 ounces per week.

[Slide.]

So the core of the advice involves two parts; for pregnant women and women of childbearing age, avoid swordfish, shark, king mackerel and tilefish which have the highest levels of about 1 part per million. We also say, for children and for lactating women, to follow this part of the advisory, not because we have any specific information on either group.

Remember, Faroes is a prenatal study, not a postnatal. But, because of the hypothesis and because of what we know about neural development postnatally, we thought, as a matter of prudence that we would advise children to also avoid the same species and, because of the lactation issue, as Dr. Grandjean did point out, methylmercury is transferred via lactation. But as Mr. Clewell, Harvey Clewell, did point out, the amount of transfer is not that high.

But, as a matter of prudence, we said, for lactating women, avoid these four species. And then we said consume up to 12 ounces per week of all other commercial species as long as they consume a variety. I keep emphasizing variety, variety, variety.

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This message is consistent, as you heard, with the American Heart Association's message of two servings of fish per week.

[Slide.]

The next couple of slides, what I am going to do is give you a summary of what we know about exposure. These are just some highlights. The average commercial fish weighted for consumption averages about 0.12 and that is why I pointed out that concentration in your table. By contrast, swordfish which is No. 15 and shark which is No. 16 have, on average, 1 part per million which you have already been told.

The average methylmercury level in the top ten, which is 87 percent of the commercial market, average about 0.2 So it is slightly higher. The most highly consumed commercial seafood, canned tuna, averages about 0.17. If you look at canned albacore, which is about 29 percent of the market, it has a slightly higher average of 0.25 to 0.3.

Fresh and frozen tuna, filets and steaks, average about 0.35. This was a surprise to us. When we started out looking at the revision of the advisory, we had assumed that fresh tuna would be like shark and swordfish. When we looked at the data, the data says something different than that.

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So the top twenty species represent, as I said before, 96 percent of all commercial seafood consumed in the United States.

[Slide.]

In regards to the mid-range species, this is the mid-range in terms of methylmercury levels, few commercial species have methylmercury concentrations between the low-end species, those with non-detects--and I would like to point out, when we say non-detects, if you look, you will find. If you look at a fish, you are going to find methylmercury. It just depends on your analytical capability, your level of detection.

It depends on where the animal is in the food chain. If it is higher in the food chain and it lives long enough, it is going to have higher levels. But you are going to find methylmercury in fish because it all starts down in the muck with the bacteria and moves its way up the food chain.

Aside from fresh and frozen tuna steaks and filets, which average about 0.35, the mid-range commercial species, which is grouper, red snapper, moonfish, orange roughy, saltwater bass and freshwater trout average 0.4 to 0.6. Each of them rank below the top--they are not in the top twenty.

[Slide.]

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So here is a presentation in table form basically of what I just went through starting with the most heavily consumed by percent of market share. There is your canned tuna which is about 22 percent. Shrimp, then, is about 20 percent. Salmon is about 11. Pollack is about 10. Catfish is about 7. Cod is 5. And then it really starts to tail off dramatically.

So these top species really dominate the marketplace in terms of consumption in this country.

[Slide.]

As I said, the Seychelles study has found no effects. ATSDR base their profile on their no-observed-effect level for the fetus which has a corresponding ingestion level of 78 micrograms of methylmercury per day. So that is taking the hair level which is around 15, I believe, in terms of their no-observed-effect level from the Seychelles and then back-calculating what the ingestion would be, steady-state ingestion would be.

That is 78 micrograms a day. If you look at the benchmark dose lower confidence limit, for the fetus in the Faroes, it is slightly lower. It is about 68 micrograms of methylmercury per day. But, again, their metric is blood so there is no a correspondence in terms of the two metrics. One is hair. One is blood.

[Slide.]

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So, just as a way of sort of putting this in perspective, for an expectant mother to consume the BMDL, now, which is--and I have heard this before. The BMDL is not an effect level. The BMDL, as put forth as a methodology, as a surrogate, as an alternative for the no-observed-adverse-effect level. It is not an effect level.

The BMD is closer to a low observed adverse-effect level. But the BMDL is not. It is as a no-observed-adverse-effect level. It is kind of hard to make it equivalent to that but that is what it is close to.

To reach this body burden, and this would be the highest body burden that is not associated with an adverse effect, the mother would have to consume one fish meal per day--that is about the 98th percentile fish consumer--containing five times the amount of methylmercury found in the average commercial fish in order to get to that body burden. That is the BMDL.

Based solely on canned-tuna consumption, women would have to consume two six-ounce plus one three-ounce can of tuna per day--that is 35 three-ounce cans per week--in order to attain a body burden consistent with a BMDL. So I am just trying to give you some perspective about the perspective between exposure levels and safe levels and no-observed-adverse-effect levels without the uncertainty factors. I will come back to this.

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[Slide.]

So, in summary, the low level fish contain non-detect to about 0.3. Most fish, including canned tuna--actually, it should be 0.2; excuse me--and all fish are in the top ten. The mid-level fish, which are about 0.3 to 0.6, include seven species and that includes fresh and frozen tuna. All are below the top 20 so they are in about the bottom 4 percent of the marketplace.

High levels, around 1 part per million, there are the four species which I have already told you about.

[Slide.]

The significance of this is that the average commercial fish weighted for consumption is low. It is about 0.12. To reach the Faroe BMDL, an expectant mother would have to be at the 98th percentile consumer and would have to eat a fish that had five times this level of 0.12, so about half a parts per million.

Per NHANES, the study population is below the BMDL, as you see in the figure you have been supplied, and none of the individuals within the NHANES approach the BMDL level.

[Slide.]

In an assessment that was provided by Environ Corporation, which you have heard something about by Dr. Jim Heimbach yesterday, I guess it was--two days ago; I

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have lost track of time. As he said, he based his analysis primarily on two datasets from NHANES and from CSFII.

This consumption data indicated that average consumption of canned tuna by women in the age group of 20 to 39 is not more than 1.7 ounces per week. This was what we were provided about a year and a half ago. I don't know if it corresponds with what Dr. Heimbach showed you the other day but I suspect it is probably pretty close.

Even at the 95th percentile of tuna eaters, it is less than 5 ounces per week. Compare this, again, to the consumption levels for the BMDL, two 6-ounce cans plus one 3-ounce can of canned tuna per day to get to the BMDL.

[Slide.]

So here is the figure that you have. This is an updated version. It is 92 percent of women exceed the reference dose. That means that 8 percent of the NHANES population exceed that. That translates to about 276,000 women per year who exceed the reference dose.

What I have over here is the BMDL from the Faroes so that you have a graphical depiction of these numbers.

[Slide.]

What I also put in here, again just as a point of reference, is the MRL, ATSDR's MRL. So here is the reference dose. Here is the MRL. Here is Faroes BMDL.

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Here is Seychelles NOAEL. I would like to point out they are pretty close. They are not that far apart.

So the big difference here is the uncertainty factor, 4.5 versus 10. That is the difference. These two studies, I find that really interesting. I have always found this really interesting that people portray these studies as being diametrically opposed. I find the correspondence remarkable.

To just point out, if you look at the MRL, most of the NHANES population is below the MRL. There is 1 or 2 percent above that but I don't want to go beyond that because I think that is three people. So I don't want to make a big deal about that. I think three datapoints is kind of small to make any profound statements on. But this is what it shows us.

[Slide.]

According to U.S. consumption data, about 96 percent of women who follow the advice in the FDA consumption advisory rule consume less than 12 ounces per week of seafood described in the advisory. These women should realize their methylmercury exposure, if they follow the advisory, would be below the reference dose. That is our goal here. We are trying to get that upper percentile below that reference-dose line.

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This 96 percent; you have, in your package, an exposure analysis that we did that was not presented during the course of these proceedings. I think there was a question the other day--you had a question about why isn't there correspondence between estimates of methylmercury burdens based on either dietary or PD/PK modeling. The reason is you are modeling commercial seafood consumption.

I think the estimates were like 2.6 or 2.9 which is where I would expect it. Ours came out pretty close to that. The reason is you have got to remember that upper 8 percentile, we are just modeling the commercial side of the exposure. Some of those women are heavy consumers of noncommercial species so, if you had done an exposure estimate that came out at 8 percent, I would be worried. I would be asking the question, what assumptions do I have built into my assessment because I haven't even accounted for the women who are consuming noncommercial species.

So, according to our consumption estimates, 96 percent of the women are below the reference dose, 4 percent are slightly above the reference dose. Again, this is all predicated on a variety of consumption. If a women has a dietary habit that focuses on one particular fish, then what we are trying to do is get her to not do that. We are trying to get her to adopt a dietary habit

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that encompasses a variety of consumption. That is our whole goal here.

[Slide.]

So, in summary, 96 percent of consumers now eat about 12 ounces of seafood per week which is the maximum recommended in the advisory, so they now have a ten-fold margin of safety. If they follow the advisory regarding variety, it should be much higher than 10. At a minimum, it should be 10. If they follow the advisory, it is going to be greater than 10.

4 percent of the consumers now eat 12 ounces or more per week and their margin of safety is around 8, when you look at the NHANES data. But if we get them to change their dietary habits, they will realize at least a ten-fold margin of safety.

[Slide.]

Canned tuna. Canned tuna was not mentioned in the advisory. This has gotten some visibility. It was not mentioned really based on two reasons. Number one, the concentrations of methylmercury in canned tuna are low relative to the other species, particularly the top four that we recommend for abstention.

Based on available consumption information for a few consumers of canned tuna need to reduce their intake in order to meet the advisory, the 12 ounces per week. That

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is what the data tells us. Tuna steaks and filets were included within the 12 ounces advice for seafood generally because the average concentrations of methylmercury are about three-fold lower than they are for these species, the shark, swordfish, tilefish and king mackerel that were recommended for abstention, because consumption of tuna steaks and filets is well below the top twenty. They are not in the top twenty.

[Slide.]

So, in summary, I am back to where I started. I am going to repeat these four major conclusions that we reached in going through our whole reconsideration of our advisory. The primary purpose of FDA's consumer advisory to pregnant women and women of childbearing age is to maximize protection to the fetus for methylmercury exposure.

In developing the advisory, the FDA believes that if women follow this advisory, they should realize methylmercury exposures below any tolerable safe level of exposure you want to talk about.

[Slide.]

According to the baseline data-exposure levels, 92 percent of women of childbearing age--again, this is NHANES--are already below the reference dose and they are essentially already eating consistent with our advisory

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while the remaining upper 8 percentile have less than a tenfold margin of safety. It is around, on average, about 8. The goal is to provide these women with information to that they change their dietary habits and so that they realize methylmercury exposures below the reference dose.

Bear in mind that the NHANES data came out--that data was collected before and at the same time as our advisory was issued. So it is a baseline. If you had asked these women about our advisory, they wouldn't have known about it because we hadn't issued it at that point.

Our 1994 advisory, one of the issues there was the fact that people say, nobody knows about. That is a legitimate consideration. So what our attempt is now is to get the word out.

I think I am at the end.

DR. MILLER: Thank you.

Any questions or comments? Would you rather have questions now?

Questions of Clarification

DR. MILLER: Dr. Busta.

DR. BUSTA: The data on canned tuna, the concentrations, were those based on the '93 report or on expanded report from commercial sources?

DR. BOLGER: That is FDA data. It was based on several FDA sources. It is based on that survey. I think

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you have a copy of that report. We had done a survey prior to that which we reference in this article. It was never published, though. Some additional data in terms of yearly ongoing surveillance monitoring work we do and our total diet study.

Remember, the total diet study which is an annual marketbasket has never stopped. We have always been doing that. I have heard people say, "Well, FDA has stopped measuring for methylmercury." No, we haven't. We have been measuring methylmercury in the total diet study and never stopped doing it. That has the four top species in the total diet.

DR. BUSTA: In that case, the consistency of the average 0.3--

DR. BOLGER: It hasn't changed.

DR. BUSTA: It hasn't changed?

DR. BOLGER: I think it is not realistic to expect--when you look at mercury and how it behaves in the environment, I think to look at a time span of ten or fifteen or twenty years is just too short to expect levels to change. Changes in mercury burdens environmentally will take a long time to move in whatever direction they are going to move in.

DR. MILLER: Dr. Shannon?

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DR. SHANNON: I have so many questions and comments but I will start with only one or two. I am not even sure where to start, but maybe I will start with my comment. One thing that your discussion and this discussion before you really emphasizes to me is that the root problem is that FDA and EPA are looking at different types of fish.

You went through quite a bit in terms of consumption and monitoring and probability and risk only from the seafood side. In fact, women eat all types of fish. But, as you said, that is EPA's job.

So it makes this job, the job that I think you have given us, difficult if not impossible to address. It reminds me of there was a time briefly when I was on an EPA committee that was looking at pesticide exposures in order to set tolerances that would protect children. They created a very useful concept--maybe they didn't create it, but I learned a concept called the risk cup where, really, you have to look at all potential sources and it is senseless to do otherwise.

I just find it so difficult to take everything that you have given us and understand how to use it and help give good advice when I know that EPA has another dataset, or has another source of fish that they are examining, and you are not talking about them together.

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You didn't present them together. So that is my comment. Now, having said that, let me just ask one question. The graph that you have given us has the 0.12 which you suggested we should primarily examine because that is the average for 95 percent of American fish. But the top ten fish consumed, I think you said, averaged 0.2 which would mean that--I am asking you to correct me if I am wrong--which would mean that, really, the safe level of consumption would be closer to 7.7 ounces per week versus 12.8 ounces per week. Is that correct?

DR. BOLGER: Your math is correct. But I think, when you look at consumption, you can't just forget about the other species because they are part of the marketplace.

DR. SHANNON: Top ten is top ten.

DR. BOLGER: Top ten. But there is a bottom ten, too. So they are part of the overall exposure. But if you focus just on the top ten, that is correct. That is where you end up. So I have no argument with that.

Can I just respond to your comment. Again, I would like to go back to what I was trying to say about the upper percentile. If we get this right, if we do our advisory right with EPA and the states, we will get those women down. That is what we are all after. We are trying to get their exposures down.

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So I think there is a consistency here. We are trying to say the same thing in terms of an advisory. It gets real difficult when you have so many different species and some women are heavy consumers of fresh-water and they don't eat much commercial species.

We thought about trying to do that. How do you d that? How do you model that population. Yeah; I could do a probablistic analysis. I don't know if it is going to be worth anything at the end of it. But you could try to model that, try to model a population who consume both. It is doable.

There is a response over here.

DR. MILLER: Mr. Spiller?

MR. SPILLER: Just a minor correction. 0.2 that you saw represents, of the top ten, the highest of the top ten. It is not the average of the entire top ten.

DR. SHANNON: If you wanted to be protective, you would want to use the high end; right? If you wanted to be as protective as possible?

MR. SPILLER: Again, all I am trying to do is just provide you with a factual piece of information. I think that there is a misperception that the top ten, the average of the top ten, is higher than the average commercial fish. The average of the commercial fish was

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0.12 and I think there is a misperception that the top ten average higher than that.

0.2 represents the highest of the top ten and not the average of the top ten. I am just trying to make that correction.

DR. APOSHIAN: I have one or two comments. First of all, you said the NRC National Academy of Science Committee did not come up with an RfD. Let me say that the National Academy of Science does not allow a number like that to come out for legal reasons. But, on Page 11 of the Executive Summary, the first sentence states that, on the basis of its evaluation, the committee's consensus is that the value of the EPA's current RfD for methylmercury, 0.1 micrograms per kilogram per day is a scientifically justifiable level for the protection of public health.

For the Academy to allow a number like that to be put into such an NRC report is very unusual and it shows how strongly the members of this committee felt about this figure.

I would like to just point out to the rest of the committee that I have been on many committees, NRC committees and other committees. I am probably the oldest person in this room. I would just like to say that I have never seen a committee of young people so dedicated to finding the truth and trying to protect the health of

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pregnant mothers and children in my whole career. So the NRC committee, I want to point out, was a very careful committee.

I enjoyed your talk. We have met on a number of occasions. I question the value and objectivity of some of the data that you are presenting. It is not your data, but some of the data. I think the FDA should use more non-stakeholder, nonbiased laboratories to accumulate data.

The Yost paper, I must say, would not be accepted by a peer-reviewed journal today. It lacks many of the quantitative justifications that we now require for articles. That is the canned-tunafish data that you put.

The pharmaceutical industry has--I think Larry Fischer knows the name of it. I think it is the CIT. Is that what it is called these days, Larry?

DR. FISCHER: Yes.

DR. APOSHIAN: The CIT is a commercially funded nonprofit objective institution in North Carolina, Research Triangle. I think the FDA should make use of such organizations as well as academic laboratories to get data that we can depend on. The data of canned tunafish, for example, is something that I think needs to be looked at very, very carefully.

Thank you.

DR. MILLER: Do you want to respond?

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DR. BOLGER: I would just say the issue of data reliability analytically is one we always worry about. We have been accused sometimes of not utilizing data from other sources because of our concerns about QA/QC. It is always very problematic about mixing data when you don't know how it has been derived.

But we are part of the AOAC and have been for many, many years, where they do a lot of interlaboratory standardization. So we attempt to do that. Our analysts are always mindful of that and that is something we are keenly aware of.

DR. MILLER: Dr. Lee?

DR. LEE: Actually I had a comment on that table that was up. So could you put that table back up? I want to just congratulate you on a very cogent presentation and I appreciate the clarity of what you have done.

The table kind of leads, almost begs, you to multiply your methylmercury times market share to determine what the total exposure would be in the United States. So has any consideration been given to weighing those numbers times consumption rather than just pick the top ten or the highest parts per million fish?

DR. BOLGER: I refer to our exposure analysis in '96 and the 4 percent, that is exactly what we did. We weighted consumption by market share. So we have done that

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in our probablistic analysis to try to model exposure over a 30-day time span.

DR. LEE: When you do that, do you end up with the same top four fish in your advisory?

DR. BOLGER: In terms of--

DR. LEE: The shark, swordfish, tilefish and king mackerel? Those are the most significant contributors?

DR. BOLGER: Overall, in terms of the overall population exposure. But when you do that, and you model exposure, you are below the reference dose. So, yeah; we did. If you took those four and did an exposure estimate for the population as a whole, you would get inconsequential exposures. But these are four species that have very high levels that could be consumed by members of this subpopulation group which we are worried about.

So we felt it was prudent to give that kind of abstention advice in the advisory.

DR. LEE: I might be misunderstanding what you just said. If we take those top four and multiply it times consumption, you would get inconsequential exposures to the population.

DR. BOLGER: The problem is, over the overall population. But we are worried about women of childbearing age who are pregnant. The problem is I don't know how much shark, how much swordfish, how much tilefish and how much

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king mackerel they are consuming. I can't wait for that data to be generated.

So, as a matter of prudence, that is why we gave the advice that way.

DR. LEE: But, again, just bear with me because I am a little slow here. Shouldn't we be concerned about the consequential exposures rather than the inconsequential exposures?

DR. BOLGER: We are. That is why the 12 ounces. That is why, when you look at NHANES, we are trying to get that upper percentile down and our exposure estimates indication that, for those species, 96 percent of the population consuming them are below the reference dose. 4 percent are slightly above.

DR. LEE: I am talking about the source of the methylmercury in fish. To decide what fish we ought to watch out for, I would think that the frequency of consumption of that fish should also be a factor.

DR. BOLGER: That is what we tried to do in terms of modeling--that is the 96 percent. We took that into account. The problem is we are talking about something I didn't present here so it is kind of hard. I know you have the paper. You probably didn't know it was in there but it is in there.

DR. LEE: Thank you.

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DR. MILLER: Dr. Hotchkiss?

DR. HOTCHKISS: Joe Hotchkiss. Mike, first of all, I can't not say this. I used to work for FDA. I worked in their analytical labs some twenty years ago. There are no better analytical chemists for foods than FDA. You can criticize FDA for lots of things, but not their rigorousness in their analytical work and their thought into their sample programs.

Simple lists of data don't mean much and you can go to the pesticide history. You have to look at the sampling plan and so forth. My question, Mike, is I think you did this but I didn't quite catch it. In a simple term for some consumer in this population we are worried about, either the 50th percentile or the 96th, or whatever, I tried to calculate and couldn't do it. What is the contribution for that hypothetical consumer of methylmercury from canned tuna compared to overall exposure.

In other words, does canned tuna represent 10 percent for that consumer, 20 percent or 50 percent or whatever of their methylmercury burden? What I am really trying to get at is the relative role of canned tuna into the overall exposure.

DR. BOLGER: I understand the question but I haven't done that kind of analysis. But, intuitively, you

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expect the answer to be, well, for the 50th percentile, for the average American, yes, canned tuna--I am not sure--are we talking about a population or are we talking about an individual?

DR. HOTCHKISS: We are talking about the population that we are concerned with; that is, pregnant women--

DR. BOLGER: The upper 80 percent?

DR. HOTCHKISS: Something like the same population that we considered in the NHANES study for either the 50th or 96th is one that we have focused on, for some member of that population.

DR. BOLGER: I am still kind of groping to understand what you are trying to get at.

DR. HOTCHKISS: In other words, the average fish-consuming pregnant women consumes so much methylmercury in that hypothetical sense. Of that total amount of methylmercury that pregnant women consumes, what is the contribution from canned tuna?

DR. BOLGER: Again, that is a good question. I haven't done that kind of analysis so I can't give you a number. But, of all the species, that, obviously, will be the biggest contributor because of its place in the market and its availability. So it has to be--whatever that

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percentage is, I haven't done that and I can't give you that number.

DR. HOTCHKISS: The reason I ask, it seems like, in a sense, the public-health objective, as you very clearly pointed out, is to reduce exposure for this important and susceptible population. It seems as though, just in my mind, knowing what is the exposure from canned tuna compared to the rest of the thing seems like an important one.

Let me ask you another question that maybe you are not the right one to answer and, if so, I can understand that. But, in FDA's repertoire of tools to protect public health, there are a variety of things, as certainly you and most people know in here. For this topic, FDA has chosen an advisory route. I just wonder why not something more similar to lead or other adventitious toxicants that are in food supply; that is, not some kind of action level or regulatory level or something based on GMPs or one of the other tools.

DR. BOLGER: We never set a level for lead. I am not aware of one. The only levels we have are action levels for ceramicware and brassware, I think it is. I think we ought to avail ourselves of any available risk management option we can. I think advisories are a very viable option.

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I have become convinced of this because, while they are hard to do and it is hard to get the word out, setting a level is--if you do an action level or a reg limit, which we have never done, or a tolerance--I mean, look what we went through in terms of setting a tolerance for PCBs. That went on for years.

In the meantime, you still have people being exposed. So what we are trying to do here with this advisory is get to those people as quickly as we can. Setting a level doesn't do that. It just doesn't work. You spend more time in deliberations and various exercises and you are not getting to the problem. We think the advisory is the first way we ought to try.

It is not the only way. We are not saying that. But it is the way we can affect the problem most immediately.

DR. MILLER: But there really is no reason why multiple approaches can't be used. If this is important enough at some kind of regulatory level along with an advisory might be the most effective way to deal with this.

DR. BOLGER: Again, I would say we should avail ourselves of any tool in our risk-management box that we can and that includes advisories and limits and whatever, GMPs. All of those options we are going to try to avail ourselves. But this is our first crack at it.

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DR. MILLER: Dr. Dwyer.

DR. DWYER: Back to the point that Dr. Lee and Dr. Hotchkiss we talking about. Last night, I just took Appendix 22, I think it is, an 23 and just tried to run through what the frequency--it says pounds per year and then parts per million and for some values it wasn't as good as your table.

Basically, what I came up with, because, when I am in Boston, I work in a clinic and I work with people who eat codfish and they eat tunafish but I have never heard of anybody who ate king mackerel. That is okay. You need the king mackerel in there, but I wondered about of these other fish. Just calculating and trying to see where the biggest amount of methylmercury came from, and it looked like it came from tunafish followed by pollack and a few others.

First of all, did I make a mistake? Is that a foolish calculation? Secondly, it leads me to think that maybe those factors need to be considered as well.

DR. BOLGER: More sophisticated analyses have been done and have reached the same conclusion. Again, the market is dominated by the top five so they really overwhelm the math here. So, no; your conclusion, as a back-of-the-envelope kind of attempt to calculate it, yes. But I am not surprised you don't see king mackerel. If you go to the Gulf, you may.

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DR. DWYER: Sure. That is absolutely true. The second thing; I just wanted to clarify. One of the groups yesterday said why don't you present, or why doesn't FDA present, its hazard analysis in a straightforward fashion, they said transparent fashion. Do you believe you have already done this or do you believe there might be some merit in just having a one- or two-page presentation that just presented the reasoning in a very straightforward fashion or do you feel you have already done that?

DR. BOLGER: I think we attempted to do that in the rationale, but I have no problems with taking some of what I have here and expanding on that rationale to make it clearer on what we went through in terms of how we finally decided what to do with the advisory. So that is a very good suggestion.

DR. DWYER: I am not a toxicologist and I find it confusing to have the same terms defined in many different ways by many--it seems like they are agency-specific definitions that are really the same thing in some cases. In some cases, they are not.

But it would be helpful, I believe. I don't think what you have done is not transparent. It is just that it is, shall we say, obscured by some of these different terms. I find this table very useful and it would be even more perfect if it had all of the various

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values and where they come up because I think they do come out, as you have pointed out already, pretty much the same.

DR. MILLER: Just for a moment, just for a second, Dr. Mahaffey wants to pose a correction on something.

DR. MAHAFFEY: Thank you. I am Kate Mahaffey from USEPA. I am one of the people who developed EPA's 2001 reference dose. This is based on the recommendations from the Academy committee that Dr. Aposhian has described. A benchmark is not--I repeat, is not--a no-effect level. As put out in the description by the Academy in our public peer-reviewed, this is a level at which the prevalence of scores on tests of intellectual development that are in the lowest 5 percent, what clinicians consider the clinically subnormal range, goes from 5 percent to 10 percent at the benchmark dose level.

This is not a NOAEL. The so-called safety factors are, in fact, uncertainty factors that represent, among other things, variability in the kinetics of mercury within the human body and in the susceptibility which we refer to as toxicodynamics.

We know, for example, the Academy value refers to cord-blood mercury. The reference dose is stated in terms of maternal blood mercury. We know that the fetus concentrates mercury beyond the blood level of the mother.

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There is variability. Some fetuses concentrate more than three times the amount of mercury in maternal blood.

So these so-called safety factors simply describe, among other things, variability in transfer to the fetus. So two points which I think are very important; the benchmark dose is not an NOAEL. The so-called safety factor we describe as an uncertainty factor, it refers to differences in kinetics, differences in tissue susceptibility and, in addition to that, could also refer to additional effects such as effects in the adult on cardiovascular disease, some emerging information on immune-system effects.

But I wanted to correct what I believe is a fundamental misconception as described by Dr. Bolger.

DR. BOLGER: No. I didn't refer to the BMD as a NOAEL. I said the BMDL which is the 95 percent confidence limit is defined closer to the no-observed-adverse-effect level. This was put forth by Kenny Crumb in 1984. The BMD is the mean central estimate. I am not referring to that. I am referring to the 95th lower confidence limit is defined as being roughly equivalent to the no-observed-adverse-effect level. That is right out of the literature, Kate.

DR. MAHAFFEY: I would refer you to the Academy report. A great deal has happened since Kenny Crumb's work

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in 1998 and perhaps Dr. Aposhian is in a good position to address what the Academy was describing.

Thank you.

DR. BOLGER: I just refer to the literature. Chris De Rosa, do you want to say anything?

DR. DeROSA: My name is Chris DeRosa with ATSDR. Having had some experience with benchmark dose analyses over the years, I would agree, as I presented in my materials two days ago, that the BMDL is essentially equivalent to a no-observed-adverse-effect level. I think that is commonly recognized.

DR. MILLER: We have got to get on with this. This debate, I suspect, can go on for a long time and that is not going to give us any more clarity to answer the questions that we are here to answer.

Dr. Russell?

DR. RUSSELL: I need to go back to the drumroll about the tuna. We have been told and read that, according to the NHANES data, that about 77 percent of the female population capable of becoming pregnant has a margin of safety, if you will, of less than 10, 8 percent. That is using the EPA RfD.

Have you modeled, and I think you probably have, of what percent of that--could you bring that down, that percent, down to 3 percent or something like that by coming

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out with an advisory to say not eat more than 6 ounces of tuna per week as some of the states have done.

In other words, I am trying to get that number down from 8 percent down to something less than that and would say an advisory on tuna, since it is so commonly eaten, would that bring that number down so that you had, say, only 2 percent?

DR. BOLGER: You are saying be more specific in the advisory in terms of the variety message, say 6 ounces of tuna and 6 ounces of other fish

DR. RUSSELL: Something like that. I am trying to do it and I am concentrating on tuna because it is so commonly eaten and I don't know what impact that would have. But I am sure it could be modeled so that you could find that out.

DR. BOLGER: I agree. It could.

DR. MILLER: Dr. Nordgren?

DR. NORDGREN: My question has been answered.

DR. MILLER: Thank you very much.

Dr. Acholonu?

DR. ACHOLONU: I just want to clear the air. Some critics of the work done by FDA say that there are some discrepancies in your results especially with respect to tuna where we talk about size, where we talk about age,

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the younger one, the older one having more accumulation of methylmercury.

They feel that the discrepancy comes from the fact that they are not sure that you were measuring the length of the fish that you used to work nor did you try to determine the age. How do you react to this criticism, and do you have any data to show that you measured the length of the fish that you worked with?

DR. BOLGER: I can't measure the length in the canned tuna so that is sort of off the table. When we go to the marketplace, a lot of times we sample what people actually buy and consume. Getting that kind of information is--you have to have a good reason to ask the investigator to do it because they always want to know why. You are asking me to gather information. What are you going to do with that?

I am not really clear what I would do with that. Particularly if I am looking at filet, again, I can't do that. We attempted to try to model that; in other words, looking at tunafish, to look at length. How you figure out the age is--I am not a fishery biologist so I don't know how you figure out the age of a tuna, but I am sure there is some way that that could be done.

We relied on NOAA to give us some input on that. When we went through that exercise and then looked at the

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actual level, we couldn't get a good correspondence. In other words, our predicted value did not correspond very well with what we actually saw in that animal based on length and age.

So, while there is sort of this general feeling that the longer the animal lives and the bigger it gets, it is going to have more methylmercury. As a general rule, I have no arguments with that. I think it is absolutely true. But when you actually try to model that and try to use length as a surrogate of methylmercury level in the fish, it doesn't really work out very well.

I think you have to actually measure the methylmercury in the fish.

DR. ACHOLONU: If that is the case, some of the advisories you have make reference to young fish, small fish, canned fish, not the filets. If you don't have that kind of data, why should you put out that kind of information in any of the advisories?

DR. BOLGER: It is not our advisory. You are talking about the states, I think.

DR. ACHOLONU: I don't know which, but--talked about young and smaller fish, canned tuna, as opposed to filet or older tuna, that the older ones have more accumulation of methylmercury than younger ones and that it is safe to eat canned tuna and not eat the big one.

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DR. BOLGER: Again, we make sort of a general statement that the longer-lived, larger animals, like shark, swordfish which are on top of the food chain, accumulate methylmercury. That is all that statement referred to.

But, to get down to specifics, looking at individual species, particularly like walleye or bass or these other species, then I think it becomes more problematic. But that is all we say in our advisory in that regard. We don't make any more statements about size because when the consumer goes to the marketplace, they buy a filet, they have no idea what the size of the fish is.

DR. MILLER: Dr. Friedman?

DR. FRIEDMAN: Yesterday night, I came across this release from the National Academy that makes it very clear that there are lots of uncertainties, that the whole issue depends on knowledge about the relationship between the predictors and the outcomes. Actually, we don't know an awful lot about that. One needs to learn about the process, as far as ages and so forth and individual differences and regional differences.

And here we are haggling over the level based on the best information that is available not coming from the United States, even, most of it and what comes from the United States is not connected to neurobehavioral outcomes.

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I am asking myself first whether you are planning on having this advisory as only a temporary measure until such time, hopefully shorter in time, at which you will have the data that is required in order to make accurate estimates.

The second thing that I am thinking about is whether, given the fact that there is so much missing information, whether we shouldn't go with the most conservative levels that are estimated because we just don't know so much.

DR. BOLGER: I think that is what we did. We went with the reference dose in terms of describing the 8 percent. So that is where we are coming at. You are talking about in terms of doing further epidemiological studies and outcome measurements? Is that what you are--

DR. FRIEDMAN: I am talking about doing epidemiological studies within the United States and being able to relate them to neurodevelopmental outcomes in young infants and children.

DR. BOLGER: The two principal investigators who are in the Faroes study and the Seychelles study, it would be better that they answer that question. They are doing the studies where they are because of the difficulties of setting up this kind of study.

I believe Gary Myers said they looked a number of studies. Dr. Clarkson is in the audience now and has spent

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many years looking around the world. That is why they ended up in the Seychelles. But I really defer to them. I mean, I think there was some effort to try to set up a study in the U.S. but I think there are so many confounding risk issues at play in any U.S. population that trying to look at these very subtle measurements of neurocognitive development, neurological development--the noise is so bad that I think it would be impossible.

DR. FRIEDMAN: What do you mean by noise?

DR. BOLGER: The background noise in the population. If you look at finger tapping and then try to measure a subtle response in finger tapping, with all the other risk issues that are at play in that population, it is very hard to measure a response.

But I would ask them. They are the PIs. I am not. I am just a user of the information

DR. FRIEDMAN: Their studies stand where they stand and this is fine. But it seems to me that, just based on the release from NAS, that information is not available. The information that they have already provided us is not sufficient. I can quote to you. It says, "Neurodevelopmental problems are the most appropriate basis for setting an exposure limit."

Later on, it says, "However, researchers still need to understand if there is a precise time during

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development when the brain is most sensitive to methylmercury and exactly how the chemical can exert its effects."

Later on, it says, "Scientists do not agree on how to account for some uncertainties such as varying individual responses to methylmercury exposure and emerging health concerns." And then there is further specification. "Likewise, research should be conducted to gather data on methylmercury exposure in different regions of the United States in specific populations with high consumption of fish."

So, if all that information is not available, you are working with approximations, you are working with a lot of unknowns, which leads me to think that, if you don't know so much--you know a lot, but you don't know enough, I would go with the most conservative measure which, to me, means the EPA measure. But, in addition to that, I think that, as a citizen, I am not satisfied with building estimates and giving advisories based on incomplete data.

I would like to have a commitment from someone, I don't know who that someone would be, or some agency that--maybe from Congress--that data will be developed in the United States to be able to answer these questions within a certain time framework. Later on, we will be able to know for sure.

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DR. MILLER: We are going to move on to the next one. That is an important comment. The problem is that it is never too clear who has got the money and the authority to do this no matter how important this is. It is something that we can include in our remarks.

Dr. Dickinson?

DR. DICKINSON: I just wondered what we know about both the frequency of fish consumption and the amount consumed by that top eight percent in the NHANES study.

DR. BOLGER: Remember Dr. Schober did indicate that they are trying to get that information but it is based on recall, how much fish. She did show you some information.

DR. DICKINSON: I remember those charts; right.

DR. BOLGER: But there is a lot of variance within that data. I couldn't remember what I ate yesterday. I don't know how people remember what they ate 30 days ago.

DR. DICKINSON: I eat tuna every day so I will know.

DR. BOLGER: There you go. You are off the chart.

DR. MILLER: Dr. Shannon?

DR. SHANNON: A quick question. As I look at this table and see that the difference between an assumed

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methylmercury concentration of 0.12 and 0.3, a pretty narrow gap, is the difference between 5 ounces and 13 ounces, it makes me wonder about the methodology here and how robust these data are.

I don't see standard deviations or confidence intervals and I even wonder if you started to include 95 percent confidence intervals around these point estimates, how much they would overlap. Is there really a difference between 0.12, 0.2 and 0.3. My associated question, which, perhaps, will answer that, is could you explain to me the methodology of doing these tests because I don't recall having heard how many fish were sampled.

I believe the analysis. I believe the analysis is accurate, but I am asking a different question. This is your table of safe levels.

DR. BOLGER: This is simple math. I was asked to generate a table using the RfD, MRL and the BMDL and then, using a corresponding level of methylmercury. Then I was asked to just pick a range of 0.1 to 1.0 and then to calculate what the corresponding grams per week would be. That is all this is.

DR. SHANNON: Right. I guess my question was confusing. But you did also say that 0.2, for example, represents what was the highest top ten; is that right?

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DR. BOLGER: No. I think it goes back to what Mr. Spiller was saying. 0.2 is the upper bound of the top ten. It is the upper bound. The average is, like, 0.12.

DR. SHANNON: So that is really the question I am asking. Is that number--

DR. BOLGER: 0.12.

DR. SHANNON: Right. Tell us about the data-collection process, the methodology. How do you know that the 0.2 is the highest top ten?

DR. BOLGER: Do you mean what data did we rely on?

DR. SHANNON: Right.

DR. BOLGER: We relied primarily on our own data that we have accumulated over the years that we put--there are three tables we posted on our website, Table 1, 2 and 3. So that is a compilation of that data that we have been generating since the '70's, really and also relying on data that was generated by NIMS in their survey from the '70's which they published.

DR. DICKINSON: Just so you know, that is Tab 22 in the notebook.

DR. MILLER: Ms. Halloran?

MS. HALLORAN: I have a question that also relates to this. In looking at this table that you gave us, which I found very helpful, it clarified a concern for

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me which relates to the margin of safety that you are providing for people at the extremes and also I might say people who are sort of unlucky in their fish consumption.

If you look at the end of the table, 1 part per million, you would reach the benchmark dose with just 15 ounces which is awfully close to 12. Now I know you are working with average figures, so you are saying mostly we are down at 0.2. But how hard would it be to get 1 part per million in a week, for example.

I went and looked at your Table 2 and you have, for the max--you give the ranges and the maximum is over 1 part per million in at least one sample for grouper, tuna, lobster, red snapper, trout fresh water and trout sea water. So it seems like you could easily eat a variety of fish and, if you had very bad luck, end up eating--follow the FDA advisory and end up eating the benchmark dose with no margin of safety at all.

So I was wondering if you had thought about that, if you have information on--you don't have that many samples to tell how accurate this range is and how often you would hit the upper ends of the range. How are you dealing with this question?

DR. BOLGER: That is in Table 2 you are looking at?

MS. HALLORAN: Yes.

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DR. BOLGER: The way we get at that is try to model our exposure based on what you find in the marketplace because the probability of getting a particular fish is determined by what is in the marketplace. Could one person do what you just said? That is possible, I presume, to be unlucky, as you say, in that one event.

But I would then say, well, okay, you would have to do that for more than just one event. If you were unlucky that one week but then the next week you ate a grouper that have a level way down towards the mean, you would have to get your blood level up.

What we are trying to do is model exposure based on what is in the marketplace. Now, there may be some markets on a regional basis where people's dietary habits are different from the norm that you see in the U.S. But that is where we try to say, well, we need to rely on the local public-health official because they are there, they have that kind of information in terms of dietary habits that we don't have.

I could come up with some scenario but I don't know how I could support it. It would just be a scenario with no basis in reality that I could establish.

MS. HALLORAN: But don't you think there should be, perhaps, more of a margin of safety so that you are not bumping right up against that benchmark dose in your advice

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in the case of data that you know of stuff that exists in the marketplace and you really don't know how frequently it is there?

DR. BOLGER: How frequently it is there, I do know. I have data on what is in the marketplace. Grouper is not even--I think it is in the top twenty so it is found infrequently. So, in terms of exposure, the likelihood that somebody would consume grouper on an ongoing basis is very remote and, therefore, it is highly unlikely they would do what you just said they would do.

I can't say with absolute certainty that one person couldn't do that. Yes; that is possible. A person could do that. But, in terms of this data, no. It tells me in terms of consumption information. That is a remote event. That is the best answer I can give you right now. Again, this is a very simplistic presentation that we were asked to put together, just to try to give people a sense of proportion and relationship here. This was not my idea. I was up until 10:00 doing this. I could have been doing other things.

DR. MILLER: Dr. Fischer?

DR. FISCHER: Just to follow up on the last question by Jean Halloran. Michael, can you tell us what percentage of the population you are trying to protect? Is it 90, 95, 99, 99.9 or just what is it? In your mind, when

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you are doing your work, how do you feel? What are you trying to do? Isn't this a tough one?

DR. BOLGER: Yes; you know better. Why did you ask it? Is this a general question?

DR. FISCHER: It is a general question, but pertaining to this project.

DR. BOLGER: I am not sure it is pertinent to this project. I think what we are trying to focus on is that 8 percent. We are trying to get the 8 percent in NHANES. We are trying to get them below the reference dose. That is what we are trying to do here, to step and ask about the percentile that--and that is a policy issue. You are trying to protect the 90th, the 95th, the 98th, the 99th.

That was not really something that we actually considered. We are looking at trying to get these women below that level. So it is a different approach. If you are asking me about food additives, well, that is another issue. But I am not talking about a food additive here, the 90th percentile that came up the other day.

I don't want to get off track because I think what we are trying to do is the 8 percent from NHANES.

DR. MILLER: Dr. McBride?

DR. McBRIDE: I have two questions. One is pretty basic. What does it mean by an action level? We

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have heard 1 part per million in fish is an action level. What action is taken?

DR. BOLGER: It is a long story. Basically, simply put, it is an advisory. It is not binding on the FDA. It is not binding on industry. It has no legal authority other than by itself.

DR. McBRIDE: So it is sort of a red flag that this is a high level?

DR. BOLGER: Yes.

DR. McBRIDE: My second question relates to--we have heard varying things and you have addressed this a little bit but I wonder if we could have even more clarification that FDA isn't any longer surveying fish content, it is still surveying fish content. Could you tell us what FDA is doing on an ongoing basis?

DR. BOLGER: As I mentioned, we are doing total diet and have never stopped doing total diet and methylmercury is in the total diet and we look at the top four species in there. So that has never stopped.

DR. McBRIDE: What do you mean by you are doing total diet?

DR. BOLGER: Oh; I'm sorry. Total diet study is an annual marketbasket that is done every year. We sample from a variety of foods. It is primarily geared to pesticides but we have some environmental contaminants

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there. So we collect marketbasket samples from four different areas in the country, once every quarter, from a different area, to try to get an overall picture of what is in the U.S. diet which is a very difficult thing to do.

But, with fish, it is a little easier, because, again, there are four fish that really dominate the market so we have them in there. Then there is the issue of other species. We had been generating some data over the years but I asked the question, what are we doing, where are we going with this, what is our approach here, what is our strategy.

So we stopped to look at what we have been generating up until that time. At the same time we were doing the advisory and that is why we generated these three tables. So Table 3 is those species in which we don't have a lot of data because we are out there getting samples and nobody had actually synthesized it altogether to figure out, well, did we have enough of this species, enough of that species, where did we need to put our resources.

So we have issued a new assignment just within the last month to go out and get more samples, more numbers, analyses of methylmercury in the species in Table 3. That is our ongoing surveillance monitoring program, in addition to total diet.

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DR. McBRIDE: One more question. This may be too particular a question to answer but, since tunafish is of interest, in canned tunafish, we gave us the mean, I think, and the range. Can you tell us what maybe the 95th percentile--I mean, the range, obviously, is the outlier, includes the outlier.

DR. BOLGER: Going back to that '93 data, I think the upper bound was 0.4 for canned tuna. 0.4. Albacore is slightly higher.

DR. McBRIDE: On your Table 2, it is up to 1.3 at the upper bound, if I am reading the table right. No; I'm sorry--well, 1.3 in fresh but it is 0.75 in canned.

DR. BOLGER: Right; but we have more data in there. I was just going back to that survey. Do we have the range there?

MS. HALLORAN: Fresh tuna is 1.3 at the top and the canned top is 0.75.

DR. BOLGER: Okay. That is the compilation of data.

DR. McBRIDE: Do you have any idea, within that, where the 95th percentile or something like that is?

DR. BOLGER: Off the top of my head, no. It is going to be around 0.5 something, I would imagine, 90th percentile. I would have to look at the distribution, if

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it is normal or log normal. But it would be around that level.

DR. MILLER: Dr. Nordgren?

DR. NORDGREN: Dr. Richard Nordgren. My concern about a lot of the things that are done--I look at the New Hampshire things for pregnant women which are using your advisory, but the average physician in our state, and I can attest the average patient in our state, will say, "Well, two or three cans of tuna. Great. I will go and eat that." But then they will go out Saturday afternoon and go fishing. So I think we have to carefully consider the effect of advisories where they are. Some states I think are very good. I don't want to make this a rhetorical question but I guess my concern is the reason the studies are not done in this country, I believe, is that we can't find an area where there aren't so many confounding data. That is the message I think I have heard today from both primary investigators.

Maybe Dr. Clarkson could comment on that. I haven't seen him for years. I don't know if I recognize him anymore. I'm sure he doesn't recognize me.

But I guess my main concern is the human organism is subjected, and especially the brain is subjected, to a lot of things. The reason we can't do these good studies in the United States is there are so many confounding

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things. The concern about the second-hit effect, a patient that has developed some problem with mercury, then later gets an encephalitis, or, in our state, drives his motorcycle off a cliff.

You can't answer those questions, I don't think, but this is one of the concerns I have. So I look at the best possible scenario, the worst possible scenario. And I look at the worst, worst possible scenario, which is a child that has been affected and then has a second or third insult. I see those people in my population every day.

DR. BOLGER: Again, I would defer to the principal investigators. I believe Dr. Grandjean is attempting to set up a study down in Alabama but he is the one you have to ask. He is the one down there trying to do it.

DR. MILLER: We are going to have to move on. Otherwise, we will be doing this when people are running for buses and we can't do that.

Dr. Friedman, you had one more question?

DR. FRIEDMAN: It is related to what was just said, the confounding effects. I think there are statistical methods that make it possible to separate--it is not that I think; I know that there are statistical methods that allow you to estimate the effects due to one variable controlling for all others if you measure them.

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The question is have people measure them and the extent to which we know about the possibility that levels below the ones that are considered unsafe may be unsafe in combination with other agents. We haven't talked much about it. I don't think there is an answer, but I think it is something that needs to be on our mind in terms of wanting the advisory to be as conservative as possible.

DR. MILLER: As far as we know, EPA is in the process of trying to develop models that allow combination of toxic substances, but, nevertheless, I think we have to consider it within the context of what data is available now. I think we all recognize that there is a lot more information we need but the recommendations we make have to be couched in the terms of what is available at this moment and not--because I don't think FDA wants to nor does this committee want to delay until the data is in. If that is the case, we have got a long way.

I am going to call this part to an end. Kathy wants to make a statement and then I am going to ask--

MS. DeROEVER: Questions were raised about international advisories. Mr. Spiller was going to make a brief presentation on the document being passed out now. But I think, at the moment, given the committee's time constraints, we will let the document speak for itself unless there are any very specific questions.

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DR. MILLER: I am going to call a break. Fifteen minutes, please.

[Break.]

DR. MILLER: We now turn away from the great fun of closely questioning our speakers to the point where we, ourselves, have to begin making some decisions. As I told you yesterday, we are going to spend some time clarifying some of the issues in three areas; toxicology, consumption and communication.

I have asked three of our colleagues to lead those discussions. Let me make just a couple of comments. Let's try and keep the discussion as focused as possible because we have got to make up some time. I realize that time is not the single most important thing but, with people leaving to make planes, it becomes a determining factor.

Also, I realize that a lot of things, from the scientific point of view, are more fun than others. But we have got to focus on the questions that the agency asked us to deal with. I don't think that, as interesting as it was, a rediscussion of the Faroes versus Seychelles will take us much more down the road to where we want to go.

So let me turn to Dr. Fisher who will lead the discussion on the toxicology data portion of this. As I said, please keep our questions focused on things that will

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help us in coming to whatever conclusions or recommendations we are going to make in terms of the questions that have been asked.

Toxicological Data Discussion

DR. FISCHER: What is toxicology and what is something else might be a little confused, but I think it might not be a bad idea for us to think about the toxicology of methylmercury and to make comments or raise questions that are important relative to exposure to methylmercury via fish consumption.

So I just wrote a few things down that might help to start the discussion but I think if anyone feels that there is an important or necessary feature of methylmercury toxicity that we need to bring up in relation to our task, please do so.

I think it is fair to start off by saying methylmercury toxicity is under study at this time relatively intensively, I would say. It certainly has been studies a lot in the past so we know quite a bit about methylmercury toxicity.

Dr. Bolger has summarized some of the toxicity, some of the most important parts of the toxicity, for us, I think, in his presentation and in the documents that he has provided. But I think some factors in the toxicity we don't know much about at this point. I think the

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mechanism, the molecular mechanism or biochemical mechanism by which it causes alterations in the nervous system or development of the nervous system, are not well known at this time although they are under investigation.

Whether it has to do with alterations of calcium homeostasis in neurons, particularly granule cells of the brain, seems to be possible because of data obtained in laboratory-animal studies. I know Dr. Bill Acheson at Michigan State and others believe that the granule cells are a primary target simply because, in experiments in vitro in isolated granule cell versus other types of neurons, granule cells were particularly susceptible and sensitive.

But the question is will the knowledge of mechanisms help us with the kinds of decisions we are trying to make today. I think it would help some but, in my opinion, it doesn't get us out of making a decision today regarding relatively safe levels of methylmercury.

Another thing we don't know much about is modifiers of the toxicity of methylmercury. Selenium comes to mind but, in fact, we probably don't know much about other factors, maybe in the diet, that can modify the toxicity of methylmercury.

One thing, of course, that comes to mind and very relevant is PCBs and how they interact with methylmercury

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as particularly important because of the Faroe Island data, of course. Some studies are underway around the country regarding the toxicity of methylmercury in combination with PCBs. These studies are going on--well, I am not sure I know of all the places they are going on but I know one, for one, that Rich Seigel is doing experiments in laboratory animals and in vitro studies with isolated nerve cells, granule cells, looking at the combination of methylmercury and PCBs to see if they are interactive.

He has published two papers so far which indicates that there seems to be a synergism between methylmercury and PCBs. The way he measures this is he looks at two different things. He looks at the release of dopamine from isolated brain tissue in response to methylmercury exposure and PCBs and each of things alone, PCBs alone and methylmercury alone, and finds that, at exposures of methylmercury where he sees no effect on the release of dopamine, if he adds PCBs to the methylmercury, he sees a great response or a larger response on the dopamine.

So the presence of PCBs seems to be augmenting the activity of methylmercury to release dopamine from nerve cells, dopamine being, of course, a key neural transmitter.

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He also has looked at calcium, intracellular calcium, in granule cells and finds the same thing, that when he puts PCBs and methylmercury together, the methylmercury-induced release to methylmercury-induced increase in free calcium in the cell, which is a trigger for many cellular events, increases.

So these are two important pieces of information, I think, that lead us--just a beginning--that leads us to begin to think that maybe there is some interaction between those two chemicals that increases the toxicity of one or the other.

I asked him whether he thinks methylmercury is increasing the toxicity of PCBs because PCBs do the same thing as methylmercury in the systems he is using. They affect dopamine release and they also affect calcium, free calcium, in cells.

I asked him whether the effect is due to methylmercury or PCBs. He has no idea at this point. He doesn't know which chemical is augmenting the activity of the other chemical. He hasn't been able to sort that out yet but there does seem to be this interaction.

But these are in isolated tissues, in isolated cells, at higher concentrations of PCBs that you always tend to use in in vitro experiments. So the relevance to what we are thinking about is a huge jump. There is a huge

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jump in trying to think about this in relation to what is going on in vivo and in the human, again.

So that is where we are with those modifiers.

I have got some other things written down here that I think are relevant. We don't know, and we talked a little bit about this--I think the evidence, the data, relative to when is the critical window during development at which alteration by methylmercury takes place.

We really, I think, haven't clarified this sufficiently. We think it must be later in gestation rather than earlier. But I think the studies that have been done really are not sufficient for us to be very certain about that.

So we suspect, I think, that it is later effects. The more subtle effects we are looking at, probably it makes more sense to think that they occur later in development rather than earlier. Earlier, there would be gross alterations in the brain. One would think that wouldn't be very subtle. But these effects, certainly, must be subtle of the lower exposures that we are looking at and the effects that we presumably see.

I think we don't know whether there is a threshold for the effects of methylmercury. Dr. Clarkson is here and, if I am misspeaking, I hope he will certainly clarify things for us.

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I think methylmercury and lead probably share this problem of not having a threshold. I think there must be a threshold for the detectability of the effects of methylmercury as, perhaps, there is for lead although we haven't really seen it with lead yet. But it is entirely possible that there isn't a threshold, meaning that there is some effect probably not good of very, very low levels of methylmercury as there is, perhaps, with lead.

If that is the case, and this is what I often tell my students, these things may be attenuators of human abilities that we just have to live with. It really wouldn't be any different than poverty or disease or other attenuators of human ability. I think we have to think of it, perhaps, in that way eventually.

I am not saying that there is no threshold. I am saying that the possibility should be thought about.

I firmly believe, as a person who makes measurements and relies on interpreting data from those measurements, when it comes to exposure to methylmercury via fish consumption or any other way that we ought to be thinking about measuring that exposure in the most direct way we can and that would be to measure methylmercury exposure in humans.

Even if we have to take money away from measuring methylmercury in fish, I think we ought to do that. I

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think we ought to do that and we ought to start measuring it in the human population in an organized manner. It is sort of silly to guess what exposure is based upon fish consumption and so on when, in fact, we can get a much better idea of what it actually is by doing--my favorite is hair analysis.

Somebody told me the other day, yesterday, it was, that he thought I should start in Michigan by getting the state to monitor methylmercury or mercury in hair the same way we measure blood lead. I think that is a good idea.

I'd love to see Michigan do that.

It is perhaps going to be done in Alaska, we heard. That is to be applauded. So I think we ought to stop messing around and start measuring exposure directly. Then we don't have to worry about ounces of fish in tunafish cans, and so on.

I am not even going to talk about RfD and MRLs and BMDLs and all that business. We have discussed that enough but that toxicology certainly is important.

Finally, I will stop and ask others to contribute by saying that no matter how much methylmercury is in the hair of the mother or in the blood and the cord blood or even in the blood of the infant, we still haven't an idea about what the concentration is at the target. Just

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because methylmercury levels seem to be higher in fetal blood and in maternal blood doesn't mean we know what at concentration is at the target.

So when we think about fetal blood or material blood or material hair, we have got to keep remembering that no matter whether we know those values or not, we still don't know the target concentration. So all of these other measurements we are making are indirect, in a way, from where we would really like to know what the concentration-response relationship is. We probably never will know this, folks. So I realize that we have got to do the next-best thing. So I am getting back to measuring.

So I am asking for other comments from those who want to talk about the toxicological aspects.

DR. HOTCHKISS: Very briefly, this committee's role, at least as I understand it, is to advise FDA. Scientific committees, in my twenty-some years of experience in doing these, always make--you can always count on one recommendation; that is, that we need better data, a rather self-serving recommendation.

But the committee must understand that the Food and Drug Administration lives in a real world at which they are under statute required to make decisions based on the best available data they have at the time. I think, particularly germane to this, is--at least, I agree and I

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haven't heard anything that would convince me that it is known whether or not there is a threshold for methylmercury, in that situation, I think that FDA's position has to be that there is not a threshold unless that data to the contrary is presented to them or toxicology to the contrary.

Given that uncertainty and some of the other uncertainties, then I think FDA's position has to be to reduce exposure to the lowest possible level while recognizing that they cannot ban fish or other products from the market, that they have beneficial roles. So I think our role is, given the uncertainties, what is our best advice to the agency now and, certainly, part of that advice is to gather this kind of information.

But, still, a decision has to be made by FDA with the data that is currently available.

DR. MILLER: Can I rephrase that a little bit? It seems to me that, in this term, one of the questions we need to ask ourselves is are there any other aspects of the toxicology that we believe FDA has not considered in establishing its advisory.

I think the debate over whether the RfDs or any of the other numbers is really a technical debate. The fact of the matter is that the variation and the uncertainty in all of these is that all of these are

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reasonably conservative. But does it have to be even more conservative, I think, is the question. Does toxicology tell us that we really have to be even more conservative and, if so, what data would we use in order to reach that more conservative position?

DR. SHANNON: One aspect of the toxicology that I think hasn't been sufficiently addressed even in the calculation of the reference dose--I looked at the monograph to be certain--was this issue of how comfortable we can feel that a cord-blood mercury correlates to a maternal blood mercury.

The way the material has been presented to us, it is along the assumption of a 1-to-1 correspondence. I think there is a very significant knowledge gap there in knowing whether or not it is truly a 1-to-1 correspondence and if, as I suggested yesterday from what I have heard, that the cord-blood mercury is going to tend to be 50 percent higher than the maternal blood mercury, then we need to know that and we need to adjust what we think the safe level of maternal blood mercury is.

So I see that as an important knowledge gap that really needs to be addressed in some way, shape or form and considered very, very fundamental to what it is that we are here to try to accomplish.

DR. MILLER: Dr. Aposhian.

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DR. APOSHIAN: I never thought I would bring up a cliché, which I am going to do in a few minutes. I was on the NRC committee for arsenic as well as the NRC committee for mercury, methylmercury. I must say that one of the results of the arsenic committee, or one of the recommendations of the arsenic committee that was quickly followed was that we don't have enough information on certain aspects of human arsenic toxicology in the United States.

I must give the EPA credit that, within one year or a year and a half of the NRC report, $3 million was immediately available on a competitive-grant basis to do the study. I would like to see--as Dr. Fischer said, we need information. I would like to have the FDA think about supporting such research grants. That is a cliché. I apologize for it, but there isn't enough money available for it.

The other point I would like to make as a toxicologist is methylmercury is not alone as far as human exposure to mercury is concerned. We certainly have mentioned that the mercury from amalgams is still a major source of exposure. There are small amounts of mercury in food and other sources and it is very difficult to separate--Dr. Clarkson and I were talking about this--the toxicology of what happens in the brain as far as the

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methylmercury conversion to inorganic mercury and the amount of inorganic mercury or elemental mercury coming to the brain.

I think no one in this committee would argue that methylmercury is toxic. I don't think anyone on the committee would argue or question that pregnant women, women of childbearing age, young children, should be protected. The crucial question is what is, perhaps we should say, the threshold, what is the dose that we are concerned about.

Unfortunately, no one knows what that dose is. Unfortunately, you are going to have to make a decision without knowing what that crucial dose is. However, I do want to remind you that you are talking not about laboratory animals, now. You are talking about human beings. You are talking about women of childbearing age. You are talking about children who have a developing brain even after they are born.

I would like to urge you to consider the ramifications to the future children. I would like to urge you to be conservative. Now, different people have different definitions of the word "conservative." I would just like you to be careful. I think that there is no question that both Dr. Clarkson and Dr. Grandjean have

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shown in all their studies--I am not just talking about the Seychelles or the Faroe Islands.

There is no question about the toxicity of methylmercury. There is no question methylmercury comes from fish. No one has said that we should not eat fish. The big question is how are we going to inform the pregnant women, how are we going to inform the women of childbearing age as to what or how much fish they should eat.

DR. MILLER: Dr. Dwyer?

DR. DWYER: I am not a toxicologist nor a neurologist so--my betters haven't asked it and I will just ask it. I am puzzled by the focus on the third-trimester effects. If it is a heavy metal and it is like lead, you would assume that there might be some effects earlier on or other fetopathy other than this one. It is a question.

DR. FISCHER: I guess I brought it up because the recommendation usually is we need to reduce exposure on young women of childbearing age. If you consider the benefits of fish consumption on the individual and, perhaps, even, some benefit coming in development, if you consider the risk and the benefits, then to have young women who are not pregnant or are about to get pregnant not eat fish, which has some beneficial effect, it might be not the right advice.

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If we knew exactly when the window was, we could restrict consumption and blood levels during that period of time, getting the benefit of fish consumption at a period that they are not so susceptible. So all I am thinking about is the window and when it is there. I don't think we really know.

DR. DWYER: I am fairly well aware of the research by EPA on DHA. I haven't looked at it for three years, but Sangiovanni and several others and I did a metaanalysis of that. I am not sure that I am as convinced that this is absolutely an essential thing. I think there are other ways of getting.

I am just concerned about these other early effects. Are there any? Or are the neurologists and toxicologists worried about effects in the first trimester as well.

DR. MILLER: Johanna, if the advisory covers women of childbearing age, it will cover that issue as well. While it is important to know whether that response is more sensitive than the response development--but that is an issue you don't know. So, for the moment, using the endpoint and applying it to women of childbearing age, you are going to cover all three trimesters.

Dr. Friedman?

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DR. FRIEDMAN: Dr. Fischer said something very interesting about the fact that we have to live with a lot of ill effects on the development of children--for example, the effects of poverty--which made me think about the possibility of looking in the Faroe Island study at the relative effect size of the methylmercury compared to poverty, if there is enough variability in the society, or maybe maternal education or something like that so that we get a feel for what it means to have those significant results that exist there.

When the results are statistically significant, you don't know if they are clinically significant, really. And also you don't know how they sit relative to other effects. So this would be something that would give life to what we are talking about.

DR. ACHOLONU: Dr. Fisher, this may be a minor point but when you are talking about the synergism between the PCBs and methylmercury, what came to my mind was the PAHs, the polyaromatic hydrocarbons.

In Mississippi, we have done sediment analysis of water, lake and river, and we know we have benthos like clams, shrimp, crabs and the rest of it. They have a possibility of taking in some of the PAHs which are detrimental to health. Has anybody done any work on the PAHs because we have talking about the PCBs.

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DR. FISCHER: There has been some work on that. PCBs are mixtures as they are in the environment. They are a mixture of a lot of different congeners of the PCB molecule. There are two classes of PCBs. One are the dioxin-like PCBs and the others are the non-dioxin-like PCBs. The chemical structure of the congener is involved in producing either dioxin-like activity or other activity.

It turns out that the non-dioxin-like PCBs are those that are active in altering calcium and dopamine release and so on. So these non-dioxin-like congeners of PCBs are probably causing the neurotoxicity.

PAHs are dioxin-like. We have looked at this in a preliminary way and can't find any effects on calcium and so on similar to what we see from the non-dioxin-like PCBs. So I think maybe PAHs are not of as much concern as PCBs of the non-dioxin type.

DR. MILLER: While it is probably highly likely that a number of factors may be acting simultaneously to do this, I think, for the purposes of our discussion, it would be prudent for us to consider all of the effects that we are looking at as being associated with methylmercury unless we have some other way of quantifying that effect.

I am not trying to downgrade the importance of this. I am just trying to say within the context--I am trying to focus on what we have to do. I think that

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assumption is the one we ought to make, that all of the effects that we are talking about come from methylmercury and, until demonstrated otherwise, that is, I think, the assumption that the regulatory agencies ought to make for this. I would suggest that.

Ms. Halloran?

MS. HALLORAN: The FDA advisory addresses just pregnant women and women of childbearing age. The Wisconsin advisory and others also address children or young children. I wonder, based on the toxicology, what we know about that and whether we think the FDA advisory should be extended to young children.

DR. FISCHER: I will answer quickly and say that I think it is reasonable to extrapolate from what we know to this situation, methylmercury in young children, to the point where we should be concerned about young children. I can't remember the exact wording of FDA's advisory. Do they specifically exclude young children?

PARTICIPANT: No; they say that this should apply to nursing mothers and young children, also.

DR. FISCHER: So we are okay there. I think that is very reasonable.

DR. APOSHIAN: I would just like to agree with Dr. Fischer. I would like to just point out an axiom that we use in teaching toxicology, and that is, children are

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not small adults. The metabolism of children is quite different and they should be considered, as the NIH now does consider them to be, individual different biological specimens than an adult. I think it is very important for us to remember that.

DR. MILLER: That is like the other one we use in toxicology; man is not just a large rat, except in personality. [Laughter.]

Dr. McBride?

DR. McBRIDE: I am struck with the fact, of course, we have to live with some uncertainty and more data would be great. Amongst the uncertainties that I also feel are there are the whole issue of maternal levels in a pregnant woman versus blood levels--we know that the mother's blood level goes up a lot more than her weight--sorry; her blood volume goes up more than her weight.

That may or may not offset what you were concerned about or maybe there is some other factor, maybe because of varying proteins or something. So that is another thing we don't know.

The other thing I think we don't know, it hasn't been within the scope for us to hear about, but there are some allusions to, is the beneficial effects of DHA and so on and when is the window for that. Unfortunately, this is not like lead or alcohol where it is easy to say don't have

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any exposure for X amount of time. This is a substance that comes packaged with some things that may be very--well, that we know, in some situations, are very good. So our task is even harder.

DR. MILLER: It makes the advisory that much harder to do.

Dr. Nordgren?

DR. NORDGREN: I need the help of our toxicologists. We are talking about the developing brain, but one piece of data that I am concerned about is is the sampling of the intake of the fish adequate to come out with an advisory like this.

There is input. There is output. Things go into the body. A pregnant women is also a different physiologic situation than a newborn, a fetus or a child. But I am concerned about--I see, that was presented yesterday, in king mackerel with a large sample of the range going from 0.2, I believe, to 2.5 parts per million. That was my recollection.

Do we see this tremendous variation in other fish by site location? I know the Alaska data suggests that it is different for many of these fish and where they are at. The Wisconsin presentation was excellent about not commercial fish but are we absolutely convinced that the consumption data on what I think are inadequate sampling is

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something we can base an advisory on? That is the question I am asking.

DR. APOSHIAN: Can I just say, as a person who, for the last two weeks, has thought nothing less--the major concern has been reading the material that has been sent to me and my dear wife who is a superb assistant of mine has gone to the library. We have an Ag school with a tremendous amount of--we have one of the best libraries in the country. I think we are in the top ten of university libraries.

The impression I have, and I think your question is a very good one, is that the sampling has not been adequate, that the FDA does not have enough money and has not gone out and sampled. The FDA, as I understand it, because of the lack of funds, depends on information that is given to them by the industry.

For example, I was impressed when I talked to--I think he is the President of the American Tuna Association. He told me that every batch of canned tuna is analyzed for methylmercury. But I would like to know what happens to that data. I don't think the FDA has the accumulated data of the American Tuna Association for the amount of methylmercury in their various fishes.

I think your point is a very, very good one, to question the amount and quality of the data that is

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available. However, regardless of that, we all know that methylmercury is toxic. I certainly would not want to say, because we don't have the data, we are not going to warn pregnant women and women of childbearing age. I am sure no one on the committee would want to do that.

However, we still have to come to a decision on how we are going to convey to the future mothers of our country and the future children, how are we going to convey to them information so that they will be able to make a decision on their own. I don't think that information, at the present time, is available to the FDA nor to this committee.

DR. MILLER: You mean how to deliver that message?

DR. APOSHIAN: I think the point was made how can we deliver a message when we don't have adequate data. I think that was your point; isn't that correct?

DR. NORDGREN: My concern is are we making decisions on the basis--I have been thrashing with this for days and weeks, but we are making decisions on some excellent studies in other population bases. But then I look here and we are seeing the discrepancy from various--and I am trying to listen to all of them.

Other people have done sampling in various areas of fish that show a wide variation in levels. As a

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toxicologist--I don't know. We talk about computer garbage in and garbage out. An advisory when we don't even--do we really know this is something we can base our recommendations to when the level of variation we are seeing in other studies where there are larger samples, at least that I have been presented with, is much wider than what the FDA--to my impression. I just haven't had time to study this issue but I am very concerned about this part of things and I am very concerned about the communication then, what happens afterwards, which is my biggest concern.

DR. MILLER: The bottom line, though, is that the FDA has to do something. I am reasonably certain that they would love to have a lot more data, too, or they wouldn't be in these arguments, otherwise. So they have got to something and they have got to do something within the data that they have. As Dr. Aposhian says, I don't think anyone argues that the effect is there, and the effect occurs at relatively low levels. Where that level is, nobody knows. And that you have to work with the data you have got.

That is one of the problems of being in a regulatory agency where even a decision not to do something has to be defended. That can't be done.

DR. HOTCHKISS: Joe Hotchkiss. Our learned chairman is absolutely right in raising the issue of are

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there parts of toxicological data which, perhaps, have not been considered or should be considered in greater detail.

A couple of facts. It seems to me we are talking about a neurotoxin here. No one disputes that. We are talking about particularly toxic effects on development, neurological development. I am not a neurologist. I am on shaky ground here, but my understanding is that that development does not stop at the time of birth.

It is clear that methylmercury occurs in breast milk although at apparently lower levels than serum levels. So you have a developing nervous system in an infant who, if they follow guidelines, are going to get 100 percent of their dietary intake from breast milk for a significant portion of their development.

One wonders, if you are going to expand the advisory, if you would expand that to lactating women.

DR. MILLER: That is still women of childbearing age. They are still being covered.

Ms. Halloran?

MS. HALLORAN: I am sorry to return to the point about children. Maybe I am really blind but I am looking at the consumer advisory for March 2001 in Tab 20 and I don't find anything about children in there.

DR. DICKINSON: The last line on the first page.

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MS. HALLORAN: In young children not to eat these fish. So then what about the 12 ounces? Is that in there? My concern here is that if the whole thing applies also to children, then there ought to be appropriate advice related to the smaller body weight of children, so that the 12-ounce restriction for a small child might be a 6-ounce restriction. Thank you.

DR. MILLER: Dr. Shannon?

DR. SHANNON: I was just going to make a comment that goes back to what Dr. Nordgren says. One thing, and you, Dr. Miller, even, said that the data we have is the data we have. I think an issue here is not the data that FDA has but the way they presented it. What I mean is that any good scientist, when they hear about sampling estimates, want to know how confident you are that that sampling represents an entire population.

The general way one does that is to hear the point estimate with some surrounding confidence intervals. I don't remember, in any of the three days, ever hearing, for example, in the case of tuna, and hearing what the averages were, what the 95 percent confidence bounds were around those estimates which I think we kind of need to know.

DR. MILLER: I agree. I am not debating that. There are two issues here. One is the recommendations that

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we make to the agency. One of the questions to deal with is the question of monitoring. It seems to me that this committee can make recommendations for substantial increases in monitoring for the purposes of determining what the appropriate statistics are.

On the other hand, does this agency not do anything while it is collecting that data?

DR. SHANNON: They have the data. They chose not to present it to us in that fashion.

DR. MILLER: I think what isn't clear is how much data they actually have.

DR. SHANNON: If they have provided us means, and they have sample sizes, you should be able to come up with some measures of central tendency and confidence intervals around that; right?

DR. MILLER: That's true.

DR. SHANNON: We never got that.

DR. MILLER: So what do you suggest?

DR. SHANNON: It certainly would have been nice to have heard that over the last three days.

DR. MILLER: That's true, but, given the fact that we haven't, then what?

DR. SHANNON: It makes our job tougher, doesn't it?

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DR. MILLER: That is why we get paid all this money.

Dr. Bolger? This will be the last comment. We are going to have to break for lunch because lunch is going to be on the table an noontime.

DR. BOLGER: What I can do, because you brought this up before, is refer you to the tables where we do provide, I believe--and, again, I haven't looked at it in a while--the ranges of residue data that we have found.

DR. SHANNON: If you are referring to the '93 article--

DR. BOLGER: No, no, no, no. I am talking about the tables on our webpage. We do give you the mean, or average, and the range, lower bound and upper bound. We didn't present it as a distributional analysis, 95 percent, 90 percent. We could do that. That is a recommendation you could make.

DR. MILLER: I am going to adjourn for the moment. I don't know if it is going to be possible, but if you can get back here in 45 minutes because we still haven't gotten through the other issues and we haven't gotten to the--I am going to make a proposal about how we might approach dealing with the questions that might be a little more efficient.

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[Whereupon, at 12 o'clock p.m., the proceedings were recessed to be resumed at 12:45 p.m.]

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A F T E R N O O N P R O C E E D I N G S

[12:50 p.m.]

DR. DWYER: I would like to just express our thanks to the staff who made these arrangements. They have really been wonderful.

[Applause.]

DR. MILLER: I am glad you brought it up now. I was going to do it later, but, by then, later, I might be the only one here.

Let's move on. The next area we want to look are the consumption data. I have been pretty lax this morning but the issues were so important and there were so many comments that needed to be made, I let it go on. But we need to really apply some discipline to ourselves if we are going to get through what we need to get through this afternoon.

I have asked Dr. Dwyer to talk about consumption data. I am going to allow about twenty minutes for that and then we will move on to the next subject.

Consumption Data Discussion

DR. DWYER: What I would like to do is go through the questions. I told Dr. Miller I was going to do this so you will hear from me only once. I have tried to focus on

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the questions and the thing I know the best which is consumption data.

[Slide.]

Just some general facts about consumption that came out in the presentations but I just wanted to mention. First of all, intakes are usually underreported by maybe 20 percent or maybe more on recalls and records. On food frequencies, it is not as clear. Sometimes, they are overreported. So there is certainly a need to validate reports on fish consumption.

With respect to the data that are now being collected, NHANES, as it goes forward over the next few years, there is something that I hope the agency explores; that is, a propensity to consume index, a little food frequency that is being tested, that will get at infrequently consumed food items. I am sure many of the people in the CFSAN are well aware of this.

It is only in pilot study now but it may roll over into the large study and it would be important for the agencies concerned about fish consumption to be sure that that gets probed in further studies.

[Slide.]

The other point I wanted to just raise about consumption was that to infer usual consumption from two or three days of records is--I believe it was Dr. Heimbach

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pointed out you need to adjust the data to pull in the tails. Otherwise, what you get is a prevalence of inadequacy of intake that is too big and, at the upper extremes, you get too many people--you don't get the right distributions.

So you have to adjust them. That is very important to do. The information that we got, as near as I could see, had done that.

[Slide.]

The questions, I believe, that were asked, first of all, were all relevant factors and information addressed sin the fish advisory on fish consumption. Remember the consumption is the amount of specific food that is consumed times the frequency of the consumption of the item times the concentration of the substance of interest.

I wanted to address each of those in turn.

[Slide.]

First of all, in terms of the food, itself, if you don't know what you are eating, if you are eating mystery meat, you can't report what it is. My own concern is that I didn't really know that king mackerel was kingfish. I didn't know that tilefish was really ocean white fish. So if I had been asked if I ate those fish, I would say no when the fact is, I did.

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That is why I was concerned about getting the NHANES item lists and so forth.

[Slide.]

So we have to know what we are eating and people have to have, in some cases, common names. They don't know these official names of the fish. The amount also depends on portion size. A common confusion that we get into is the number of servings or the number of portions that you eat. Sometimes people say, "I ate it once." But what they mean is they at six portions.

The frequency of consumption, I mentioned that it needs adjustment. Otherwise, over the 95th is not going to be appropriate.

[Slide.]

On the concentration of methylmercury, it looked like the methylmercury data was good for many but not all fish. It is important to make sure that we get good data. The thing that struck me is surprising over the course of this three days has been that, because I look at a lot of other nutrients, or I look at nutrients in food, usually, for many, many foods, we don't have very many samples, at least in the standard reference database that is used for nutrient calculations.

So I wasn't as shocked about the quality of the data as maybe some others were.

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[Slide.]

But, certainly, we need good data and we need a current single-source database that is available to professionals on all fish. This has always been difficult. At least it is hard for me to find those sorts of data.

[Slide.]

We just need to remember that the data that is most important, as far as I am concerned, is not the fish that are highest but also the fish total concentration, times, frequency of consumption, because that is going to be what Ken was talking about and others this morning.

DR. KUZMINSKI: Could you go back to that slide, please?

DR. DWYER: Right here, Larry?

DR. KUZMINSKI: Yes. What do you mean by "need to mention on fish?"

DR. DWYER: Oh; I think the advisory needs to mention not only the fish that are the highest amount per gram but they need to consider mentioning the major contributors to the total dose of methylmercury that the person has. I think the next slide might show it.

This is the back-of-the-envelope calculation that I did last night with Appendix 22 and 23. Again, I stand to be corrected, but when I did that, just taking the pounds per year and then the amount that was given in our

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book, different fish emerged as the fish that would be the ones that, if the person were an average consumer, they might be getting most of their methylmercury from.

I don't know how to handle it. It is not my place to handle it, but it seems to me that people are going to asking about that and, therefore, we need to consider that, too.

[Slide.]

What else? This whole business of filling in the database on fish, especially not only commercial fish but all fish, and assembling those existing values from state sources as well, of course there have to be quality assurances on the data. You can't just throw everything into a database.

But it would be great if it was a little more accessible than it seems to be right now to the average person who is interested in these things, 70,000 dieticians, probably a lot of pediatricians. This business is emphasizing variety and substitution I thought was great, not just avoiding fish for high-risk groups, and don't hang crepe if you emphasize variety and substitution. It strikes me that it is helpful, at least where I come from, which is where I have to give advice to people, mostly to patients.

[Slide.]

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Back to the business of some of the species mentioned are not widely eaten. It is fine to mention them. I am just saying that there are others as well. Then this business of portion size. Again, I think it needs to be standardized.

[Slide.]

I don't think most of the people I know how big commercial fish are, so this business about the size of the fish, maybe it is useful and, if it is, fine. But I just don't think most people know about it.

In terms of advisories, there has to be a way of having only one message. We went through this on food safety and there are a thousand messages from each agency. You can't get the simplest thing across. Many people--I don't mean many people at the agencies, but many consumers are not going to ask state or local experts. So, if there is some statement that can be made that also gets at the state and local issues for home-caught fish, I would personally welcome that.

[Slide.]

I suspect that you all have already done this at the agency, but I just wanted to say, for my own personal purposes, to have a hazard analysis and set the level in the advisory accordingly. I don't know where it would come out. I assume it would come out probably about where you

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are now or maybe even a little--well, let's just say about there, for pregnant and also for lactating women and children, but basically focussing on pregnant women.

It seems to me the assumptions and the math just need to be set out on a couple of pages and put into a journal article someplace where people can refer to it, just the way they did with the fortification of grains with folic acid. It is laid out in the literature for anybody who wants to see it.

It is wonderful that it is in concert with American Heart Association, but FDA is expert on food safety. The American Heart Association is the expert on other things. So, if there is a leader and a follower in this advice, the government agency has to be primary, not a voluntary health organization.

So the basic point of all of this is simply to give a transparent evidence base for the decision. I am not saying that you don't have it. I am just saying put it all together in a journal article.

[Slide.]

The second question was whether FDA should advise pregnant women to avoid any other species not specifically mentioned. To me, the rationale for this would be that the contribution to the overall dose or burden depends on the

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concentration in food times the amount eaten times frequency. The fetus is likely more sensitive than adults.

[Slide.]

So my answer to that question would be yes, include all the major contributors to total methylmercury intake. I don't know if it is tuna or pollack. As I read it, it is. But they are more common than king mackerel and codfish and so forth. So include them as well.

[Slide.]

It seems to me that if it is combined with advice to eat a variety of other fish, I know the material that was given us this morning said that it would not happen, that people would end up with both increased fish consumption and lower methylmercury intakes. Maybe it is just the same or maybe just the decrease in methylmercury intakes. But it seems to me that if everybody ate at the 95th percentile, did all the things you said, you would end up with more fish consumption.

In any event, monitoring hair and cord blood and maybe meconium as well, I think, is very important because I am not convinced of how tight those associations are because of my concern about food intake, that I know that there are a lot of errors in that. So we always like biomarkers as well.

[Slide.]

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Third, should the agency issue a fish listing as adjunct to its advisory clarifying variety? In my judgment, yes, because it helps keep consumption at the same levels, or whatever, but reduces the risk of methylmercury. My question, though, is shouldn't the private sector help on this? Isn't this something we have other people who can help to do that, extension agents, the fish industry, the restaurant people.

I don't like "good food," "bad food," approaches. So, by stressing that there are many fish and that fish have benefits, you are not hanging crepe around fish and sort of putting a black border around fish consumption. I don't like to do that for food and, particularly, to fish.

[Slide.]

What about revising the advisory to say 12 ounces includes all sources of fish, both recreational and commercial. Again, these are my own personal answers. Yes, I think from the consumption standpoint or the cells of the body, they are all the same. The cells don't know that one is regulated by EPA and one is regulated by the state and local health authorities and one is regulated by FDA.

So it seems to me that that, plus the fact that recreational consumers, I think I heard, eat more fish. There is every reason to put it all together. Just having

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something that is advice that covers the whole gemoosh, if you will, everything together, gets to the kind of thing that we have, the "know your number" for blood pressure or serum cholesterol or whatever, just, to me, makes it easier.

[Slide.]

Finally, should FDA increase monitoring of methylmercury in commercial fish to keep advice current. To me, that is a no-brainer. The answer is yes, you have got to continue the marketbasket. Consumption patterns do change. We need to keep the advice current. Methylmercury levels may also change. I gather it would be a very slow process if that were the case but, nevertheless, it is important.

It seems to me that industry needs to step forward to provide a credible set of data for the databases. This is certainly the case with a lot of industries. I am working on flavenoids right now. The tea companies have done a lot of work on that that is very credible. It is good research and there is no reason why we can't use it in our national database for flavenoids.

I was enormously impressed with the work of the states which have, it looks to me, like pretty good data on some fish that may also be useful and that needs to be

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summarized in some database that isn't just Wisconsin or Illinois or Massachusetts or Nantucket or wherever.

[Slide.]

Finally, it seems to me that the Food and Drug Administration needs collaboration and help from the state and local agencies which, in many cases, have done wonderful work. The Alaska work we have heard about, the Wisconsin, the other states, and from EPA and from other federal agencies to get this consumption message across. I don't mean just government agencies but certainly they are part of the solution.

I mentioned it should have said young children as well as young women.

That's it.

DR. MILLER: Dr. Shannon?

DR. SHANNON: A question based on your experience. It seems one problem with the current advisory is it is not very specific about young children. So I think my question to you is isn't it customary, when talking about children, first to define the age and then, second, to make weight-based recommendations so a certain amount of fish per pound or kilogram of body weight for a young child?

DR. DWYER: I defer to you as a pediatrician and to the many other experts here but it would seem to me that

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the biggest risk, if the concern is brain development, would be the first year or two of life when the brain is growing the fastest. In the first six months, I would hope that no children--they might get some exposure through breast milk, but they are certainly not going to be eating fish.

So how you word that would be something where you would want consultation with people like yourself.

DR. SHANNON: I just wondered what you are used to seeing in terms of advisories for certain patterns of intake based on weight when you are talking about children.

DR. DWYER: I can't answer it. I'm sorry. I just don't know.

DR. MILLER: Actually, most of the time, in giving out advice to the public, that isn't very useful because they don't make this calculation for foods and so on. But, on the other hand, age-related recommendations are pretty common. I think you are right. I think, in this case, it would have been better to define what a young child is.

I think somewhere I read something that said it was under the age of twelve or fourteen.

DR. SHANNON: I saw that states used a different number. I don't recall seeing an FDA definition.

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DR. MILLER: Maybe that is what I saw. Somewhere, somebody talked about an age relation, children under twelve or something like that.

Other questions or comments? Dr. Scherer

DR. SCHERER: You talked about the adding of some dimensions to some of the consumption data that is being collected. I guess, based on the upcoming discussion on risk communication, it seems to me that the one bit of data that seems to be really missing is some kind of description of who we are talking about.

I am thinking about geographic, ethnic, cultural, demographic information to help us understand who is it that are the high fish consumers. We, for example, don't know very much about cultural differences at this point and that may, in fact, be a very important target group, as I say, for the communication discussion.

DR. DWYER: That is a very good point. I think I sort of got there when I looked at some of those names for fish that looked like they were Spanish. So they would be getting at one risk group but, certainly, there are a lot of others, geographic, particularly.

DR. MILLER: Other comments? If not, thank you.

Dr. Scherer is going to talk about the risk communication issues.

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DR. SCHERER: I thought it might be helpful to kind of introduce the risk communication discussion by setting out a little bit of a framework since I assume that most of you don't consider yourselves social scientists or risk communicators.

Just some general comments. We have heard a lot about risk communication from various sectors through the last couple of days, but it probably doesn't surprise you that behavior change is extremely difficult, particularly directed behavior change. It is much more than just getting information to people, as I am sure you are aware.

But yet the bottom line of what we are really trying to do is change behavior in some way. Now, if we were selling toothpaste, that would be a relatively easy thing to do. Advertisers spend a few million dollars and they can influence 1 or 2, maybe 3, percent of the population.

What we are trying to do with this kind of an advisory, however, is a sustainable kind of change. This is something that you have to make a decision about every day, or every time you consider eating fish, for example. You have to initiate that kind of behavior. Protective health behaviors particularly are very difficult to bring about change.

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What I want to do is lay out for you the kind of framework that we often think about. It is a very simplified and quick one but the kind of framework that we think about in terms of putting together a communication strategy and, at the same time, thinking about the kinds of evaluations that are appropriate for doing that.

Obviously, the first step is to deliver the message. We have heard a lot of ideas about how to get that message to various ones through various segments, through physicians and the news media and magazines, and so forth. So the first level is getting that out.

Now, as I just mentioned, one thing that we don't know is really very much about the target audience. We don't know who they are demographically, who the high fish consumers are, particularly if we are focusing really on that upper, the 95th percentile, that are the high consumers. If that is who we are trying to target, then we are reaching a lot of people that are already eating within the guidelines and what we really need to do is to try to target those people that are above that recommended level.

I am going to give you some very general numbers but let's think about that we reach 100 people. We send our information out. It is available for 100 people. The second stage that has to happen is that we have to attract

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their attention. Something in the message has to get them to pay attention to it.

Let's say we are phenomonally successful and 50 out of 100 actually pay attention to it. That is a pretty high estimate for most studies that I am aware of. Third stage; if they pay attention to it, they have to actually begin to understand what it is saying; in other words, it has to be put in some kind of a format that it makes sense to them and they can understand what the message is.

The kind of message that we are talking about is an extremely complex one. It is not, "Go buy Brand X of toothpaste." This is a complex one and we are asking them to make judgments about a number of things.

The third, and I am simplifying a lot for the sake of time. We paid attention to it. Let's say we are at 50 percent. They have understood it now. We reach half of the people. We are already down to 25 people out of 100, that they have some kind of understand. We have a lot of research in terms of writing complex messages in understandable forms. There is a lot of research and you have heard some of that mentioned the other day.

The fourth stage. The message, in some way, has to be memorable. People have to be able to recall it at the appropriate time. Even if we have been successful through all of the other stages, they understood it, but

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when it comes to the time in the restaurant or the in the fish market or whatever, they actually don't recall the information, then we have not been successful.

So, again, if we say, well, we are successful 50 percent of the time, we are now down to twelve individuals or 12 percent.

Another stage that is often put in here is a behavioral-intention stage, that once people have gone through all of these, it is memorable, they can recall it, they actually have to have made a decision that they are going to behave in accordance with that information. So they have to go through some kind of a decision-making stage.

Advertisers get around this by simply bombarding you so much that you don't have to think very much about. You go and you buy this brand of toothpaste. This is a bit more complex that people need to think about what this really means to them. Maybe they like a particular kind of fish and they don't like other fish.

So they have to make a decision. Again, if we are successful in half the time, we are down to six. Then we have to, in fact, at the stage of some kind of action, have the behavior. Now, behavior is--one of the things that we talk about is that most of us operate on what is

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described as heuristic rules, very simplified rules that we follow in terms of making decisions.

You don't go into a grocery store and go through a whole long complicated decision-making process about every product that you want to buy. You have general rules about how you do that, how you behave, all of that. So they really need some kind of a heuristic rule.

Someone suggested, for example, a little card that you carry in your billfold, or whatever. That is sort of an aid to what I am talking about as a simplified rule. Of course, you have to recall that you have it and you actually have to have it in your billfold at that particular time.

So the bottom line is, if you kept track of the math, we are down to about three people out of 100 that we initially reached. All of these stages also are appropriate evaluation stages to try to understand where, in fact, there is weakness in our communication process.

So I guess I do that simply as sort of framework for beginning to think about the complexity of this message and focus you on the kind of recommendations that might help FDA in terms of dealing with what I consider an extremely complex message to communicate.

So I will turn it back over to you and recommendations or issues that need to be addressed.

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DR. MILLER: Any comments?

DR. SHANNON: Would you think that, just in your judgment, being that we are dealing with pregnant women, you would have a higher probability of behavior modification because they are motivated to protect their unborn?

DR. SCHERER: Another area that we could talk about is the idea of fear. There is a lot of research that has been done in terms of initiating fear to get people to behave in a certain way. The danger, it seems to me, is that if you trigger too much fear, you, in fact, cause them to not want to eat any fish. That is the simplified way of reacting to it.

If you don't have enough information to feel like you are making the right decision, then let's do away with fish. I don't think that is what we really want to have happen.

DR. MILLER: Dr. Fuller?

DR. FULLER: In a follow up on that, getting to sort of the same point, this is an audience that is, perhaps, more motivated to get information. Does that improve--I mean, what I want to say is yes, it does. Is there anything to demonstrate that it would improve, through that interest, the ability to add some--I mean, does that work in our favor to add to the complexity?

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What I am thinking is that, in a prior presentation, we were just saying yes, add species, add more information, and I think there are, in any segment of the population, people that want more information. They may be a small segment but I would--perhaps, I guess, the question is is this a population which that segment might be actually larger?

DR. SCHERER: I would certainly argue that it is. In any population, you have people that want different levels of information. Some people only want the heuristic rule. That is all they want. Other people want to look at the risk assessment. Now, granted the number that want to go all that far is relatively limited.

But simply by having that kind of information available, going all the way to the complex science, increases the credibility of the organization, that is a transparent kind of process. Here are the assumptions we made in making this recommendation.

I would certainly think, with this particular population, there would be more people who would want that level.

DR. MILLER: Dr. Montville?

DR. MONTVILLE: I ask this only half facetiously, but if we have, from the NHANES data, 8 percent of the population being over the limit, and the return on

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information input is half of a half of a half of a half, it sounds like if we do a really good job, we might push that 8 percent to 6 percent.

Is that a fair analysis? Secondarily, how are we going to know if our advisory is successful or not?

DR. SCHERER: I guess my reaction would be that we get evaluated at any of these stages. The problem is that we often evaluate it based on very early in the process; in other words, the number of pieces that we sent out or the number of physicians that we contacted.

But we actually seldom know whether the behavior change actually happened. That is a very difficult question. We have been talking about difficult toxicology questions. Getting at human behavior is also a very difficult level to try to get at and measure that.

Nonetheless, I think it is a very important process to try to do.

To answer the first part of your question, to me, the issue is focusing of resources. We can be more successful than this if we are able to focus our resources on a particular population. That is why I think it is important to begin trying to identify who is it we are really trying to change. Who are the high fish consumers?

If we know that is an Asian population or a Spanish population or in particular geographic areas, we

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can concentrate resources on that and increase the likelihood of success.

DR. MILLER: Dr. Nordgren?

DR. NORDGREN: Dick Nordgren, again. My concern is that, and you could address this, I think, much better than I can, is the mixed message. That has been raised as one of the concerns because the average--I am thinking about my patient, my colleagues, everybody else outside of this area.

So many of my colleagues and my patients, they don't know what FDA stands for. They don't know what EPA stands for. They don't know what all these initials stand for. I am sort of the naive rat in this experiment. I knew some of these things. I have learned so much this last week but I am very concerned about the mixed message.

My wife sits at home, and she is very intelligent person. She is the Assistant Deputy Democratic Leader in the New Hampshire legislature. And she says, "Another missile from Washington. What am I supposed to do for lunch today? Should I eat fish? Should I do that? Well, I guess I am not pregnant but I have already had a heart attack." She is getting so many mixed messages as somebody who has tried to meet these guidelines all along. But she doesn't know what to do.

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She is intelligent, a very intelligent women. I see my colleagues, most of them are intelligent, but, as Dr. Lockwood said, they are so busy, they don't know what is going on.

I still think back--this is beginning to sound like a testimonial--on my experience with fetal-alcohol syndrome. Michael Dorris was a very good friend of mine and I took care of his son. He talked about, "I am a writer. You are a doctor. It is your job." And said, "No; you have a responsibility as somebody that can meet the public and influence the public."

Nobody has ever disputed my statement. Michael Dorris did much more than any organization in Washington in raising the awareness of fetal-alcohol syndrome. I have never heard anybody dispute that statement.

I sort of feel, getting the message out, we need a spokesman. This is not FDA's--they are not going to go out and hire Bruce Willis, who I saw on t.v. for adoption of foster children. That isn't their role but I think, as people that are interested in these things, the consumer groups and things like that, who are very concerned about these issues, need to think about getting the message out.

That is my main concern about this but I think we also have to be very careful on the message that it is understandable it is based on data that is meaningful. I

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am very, very comfortable with the things that the FDA has done, on the data they have, but do they have enough data on what people are consuming. I am still concerned about the sampling of the fish and is that good enough and wide enough.

There have been a lot of concerns by testimony here about that issue. So I think I am concerned about the mixed message which has been raised as an issue coming out of this city. Mixed messages don't fly. I would like you to comment.

DR. SCHERER: I don't mean to be the focus, but I guess what we do know from risk communication experience is that when people are faced with complex, particularly health-risk information, and they have mixed messages, they often disregard all of the messages rather than try to take the time to sort out which one really applies to me.

It is very common for people just to say, "I don't know," and forget. So, yes; I think the mixed message is of concern.

My looking at it, and if I am correct, I think I found 2,000-some different fish advisories in the U.S. Granted, the issue is that they probably do not actually conflict. There probably is consistency. But when I started looking at some coming from states and trying to

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look at the FDA one, there was an apparent conflict on the surface.

My guess is they probably didn't really conflict, at least not much, but the tendency would be to say, "Gee; now I don't know. I don't know what I am supposed to do," and not try to really analyze whether there is a consistency or not.

DR. MILLER: Dr. Fischer?

DR. FISCHER: I wonder if you would comment on the effectiveness of labeling, the type that you find on alcohol or cigarettes. Is this an effective way for risk communication?

DR. SCHERER: I think the evidence is that it is successful for a certain portion of the population. I think alcohol, the issue of pregnancy and alcohol consumption, the labeling has been only a part of what has happened in society, that there has been a lot of general attention to that issue.

So the behavior change that I think we have seen in the last fifteen or so years--I am not sure when the labeling actually started--but we can't attribute it all to the labeling. Certainly, it has played a role in it. There is a lot of research on how people react to and understand labels. A lot of people certainly just ignore

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them totally, but there is some evidence that labels are successful in reaching a certain portion of the population.

DR. MILLER: But isn't it also true that crepe labeling works, when it is going to work, when something i yes or no?

DR. SCHERER: I'm sorry?

DR. MILLER: When something is a yes or no decision, not yes, maybe, or some?

DR. SCHERER: Oh, yes. Simpler behaviors are--

DR. MILLER: That is what makes this such a difficult issue.

DR. SCHERER: Yes.

DR. MILLER: Dr. Aposhian?

DR. APOSHIAN: The question that I had has already been answered but I want to complement Dr. Scherer for taking us through the 100 percent down to 50 and so forth. I had never heard that before.

DR. SCHERER: There are actually eleven or twelve steps.

DR. APOSHIAN: That is very, very good.

DR. SCHERER: I simplified a little bit.

DR. APOSHIAN: Thank you. It is very valuable to me.

DR. MILLER: Dr. Lee?

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DR. LEE: Actually, my colleague, Dr. Montville, lofted a 50 percent rhetorical question which I think I just want to throw a 50 percent reply to and that is how do we know if the advisory is successful. I think know if we have a measurable drop in hair-mercury levels in pregnant women.

DR. MILLER: Ms. Halloran?

MS. HALLORAN: I think, in talking about communication, just to clarify as a couple of people said, it is a tiered approach, I think, that really has to be followed. You have to have sources of information for people who want and can digest the complex information but you also need the simple methods.

I think it is in the simple stuff that we have been lacking so far. For that, one thing that could be considered are placards at point of sale that could just say, "FDA advises pregnant women to consume fish no more than twice a week," some very simple condensed message, and not to eat swordfish and so forth.

That would also, I think, have a function in heightening of awareness. I am also concerned, though, that not only is it a complex message about mercury but we also have a PCB issue and a raw shellfish issue also. Pregnant women probably shouldn't eat raw shellfish from a safety point of view.

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It would be best if, really, the government as a whole could fashion a unified message on fish consumption for pregnant women, if that could be condensed into a very small, direct message and then put out for the public. I don't think this is impossible to do. You might have to consult with an advertising agency but this is something that I could be possible.

Then, finally to emphasize getting the message together, again, I think is really, really important because consumer organizations have really not felt that the messages were unified enough and that some of them were not credible. They have come up with their own messages and this is really not helping anybody, I don't think, to have so many messages.

DR. MILLER: It seems to me that one of the major--I am saying these things to try to get ourselves a little focused as to what is coming next--it seems to me one of the almost uniform comments that have been made in virtually all of our discussions is the need for close collaboration particularly certainly among the government agencies. I won't talk about things outside government because that is harder to have to get voluntary things and people have different agendas.

But, certainly, among the government agencies, collaboration to put together an advisory that could be

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used as a model both at the state and the federal level and modified in local areas for their own particular problem but still having the same basic message.

In listening to our discussion, that seems to be it. Also, I think that the issue has come up again about how do you reach the target and there are individual suggestions that have been made. But I think the basic issue is that we are going to require every venue, every possible avenue, of communication ought to be used.

It is an important enough issue to make that kind of effort. If it means placards, if it means things at the retail level, if it means things at the media, the constant kicking of the media to indicate--you don't always have to have crepe news. There is good news in this, too, as well. That also might work as well.

But if this is important enough, it seems to me it should require an overall governmental effort and not just being left only in the hands of the regulatory agency that has that particular responsibility.

Dr. Friedman?

DR. FRIEDMAN: As I was listening to your expert advice about how to target it to populations, I was thinking that, even though there is a lot of scientific backup to all that, it seems to me that if a message becomes part of the culture in general, it is likely to be

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more effective because a pregnant women is connected at work, family network, and friends from other places.

It can only help if other people also know the message, people that are not in the target population. But I don't know if anybody looked about the merits of targets versus the merits of just making it part of the general culture.

DR. SCHERER: I would like to comment on that because that is one area that I do a lot of work in, the idea of trying to change social norms. I think we have seen that kind of change come about in terms of the "Don't let a friend drive drunk." That is a part of our culture now, and not many years ago, that was not even talked about.

Ultimately, that is what we are really talking about is trying to bring about that social change as a society so that it is a part of the social norm. People remind you that this is the kind of behavior.

DR. MILLER: Dr. Acholonu?

DR. ACHOLONU: I think Dr. Miller has answered part of my question but, for emphasis sake, what is your opinion about putting out the information on radio and t.v. with some frequency to the extent that it will enter the ears of people. There are some people who don't believe in

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reading, but they are more comfortable when they see something and when it is said on radio and t.v.

Do you think it would be as effective or more effective than the other methods we are using so far? Do you feel it would be effective?

DR. SCHERER: The general rule is if you are trying to sell a trinket once, you can do your message one. But if you are trying to bring about any kind of sustained behavior, you need frequency over long periods of time. Certainly, that is what this calls for. I think that means that it certainly has to be multimedia. It can't be just one direction.

I think the issue of trying to change the social norm suggests that, that if you only hear it from your physician, it is not going to be nearly as effective in bringing about change as if you hear it from your physician, you hear it from your husband, you hear it from the neighbor, you see a brochure at the supermarket.

That is what really begins to bring about change, that we are constantly reminded that this is a behavior that we need to sustain.

DR. MILLER: Dr. Fischer?

DR. FISCHER: I think everybody agrees we would like to have a clear, short message, the kind like we have just heard, "Don't let your friends drive drunk," to change

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the behavior. But, what I am worried about is if we get it too short like that, maybe we won't get in the benefit part of the equation.

So I think the long messages so far have put forward the information of the benefits of eating fish and then discuss the risks. I think, in any short message, we should try to get that risk-benefit information in it. So, slogans are great but I think we ought to do that.

DR. SCHERER: Absolutely. I am a very strong advocate of making sure that the science is put into complex messages like this. There is a problem of getting messages so short and sweet that you lose what they are about. Again, we are not selling toothpaste. We are selling complex science. So there needs to be enough information there that people can make some kind of judgment about the risk-benefits.

We talked about creating fear earlier. I think that is an even stronger reason for the benefits to be there.

DR. MILLER: Dr. Lee?

DR. LEE: I think we might be just underestimating a little bit the power of a recommendation from the Federal Food and Drug Administration because just, again, using an anecdotal account, the last time, when FDA issued an advisory on mercury, within a day of that

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advisory, the local news media was calling me asking where do they get mercury analyses done. They had got all these samples and they wanted to do an expose or a story.

I hope that we don't, as the scientists, try to determine the media strategy for disseminating this message. I think our calling is to determine what the message is and really depend upon the state departments of health and the consumer-advocacy groups, the university-extension personnel, the mass media, the print, the t.v., the radio. Some of the best pieces I have seen on mercury have come from print journalists.

They have a very important role in this that I think is going to occur.

DR. MILLER: Mr. Scholz?

MR. SCHOLZ: If we are talking about changing people's behavior and we are talking about them understanding the consequences, if you look at other campaigns that have been done discouraging pregnant women not to drink, other things, those sorts of campaigns are enormous. We have touched on this before.

I think that if, in fact, while we are not going to write the ads and put together an ad program, if, in fact, it is a recommendation that we should take this route, I think it is only fair that the recommendation is accompanied by some estimate of what it is going to cost.

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It is terrific to sit here and say we should run a big media campaign, we should do this, we should do this. But somebody will pull out that envelope and start to figure out what it is going to cost to do this and it could send it to the shelves to collect us.

So I don't disagree with you, but I think we have to be realistic and understand what a recommendation like this--what comes with it.

DR. MILLER: That may be true but, nevertheless, the amount of money that is going to be spent is a direct reflection of how important we think the issue is. I agree; it is not up to us nor is it in our purview to figure out where the money is going to come from because, ultimately, it is quite true, the regulatory agencies, if they accept our recommendations, and I think they will, that this is an important public-health issue and we are going to have to make some decisions on what they are not going to do in order to pay for this. And that is a priority issue of some importance.

I am going to try to get down--we will have Dr. McBride and a couple of others but then we have really got to come down to the hard issue. I think that we ought to start doing that as soon as possible.

Dr. McBride?

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DR. McBRIDE: I have two slightly different affecting-behavioral-change questions. One is, basically, I am struggling with the issue of adding tuna. For poor people, tuna is a big source, maybe their only source, of fish. We have heard that the amount of mercury, methylmercury, in tuna varies tremendously can-to-can, maybe within the same manufacturer, maybe across manufacturers. That I don't know as well.

Do you think that if tuna is mentioned as an exclusion what effect on behavior might that have in general?

DR. SCHERER: As an exclusion meaning--

DR. McBRIDE: If tuna is added to the list. One of our questions is should we add any other fish to the list.

DR. SCHERER: My concern would be that that message would have to be very carefully crafted because there would be a high risk that people would simply stop consuming.

DR. McBRIDE: Another question about behavior and this is, perhaps, out of our purview, but I think that if we are going to ask for more and continued monitoring, that that should include manufacturer name and canned tuna. I don't know if this is true. Maybe I am naive. But it seems to me that might provide pressure to some, maybe even

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to stores buying canned tuna, to avoid those that come out with the higher parts per million of mercury.

Maybe it would pressure tuna companies to throw back the biggest fish, let them breed, take the little fish. Maybe I am naive. Do you think that there is any hope of change of behavior with that sort of approach?

DR. SCHERER: I am not sure I am the one to answer how industry might react to that. I guess my concern would be how consumers might react to it. That has already been on CNN this morning.

DR. KUZMINSKI: Just a comment on that. Having spent close to thirty years in the food-processing industry but not in the fish industry or any part of it, I think--I tried last night in addressing these issues, these five questions, as to generate a position, where am I in the consideration of this whole issue and then, given that position, address answering the five questions.

Part of it, where am I, was the role by industry. I think a responsible food processor certainly wants to know, needs to know, what is in their product whether it is branded or not. This applies to the fresh, frozen or canned fish in this issue.

I was encouraged to hear that the tuna industry has anecdotally said that every batch of processed canned tuna is analyzed for methylmercury content. That is

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appropriate, in my opinion. There are examples, in my own experience, where the agency has worked with the industry and not on this issue, because I am unaware of it, but on other issues where they have asked industry for samples--not for samples, necessarily, but for data that industry might have and can be submitted through a third-party basis.

But there are historical, valid examples for industry cooperation with the agency on issues like this. So I think the history is there. It can be done. In my own opinion, the responsible food company wants to do this kind of thing and needs to do this kind of thing.

DR. MILLER: That is a case in point where agency worked closely with the industry to reduce the lead content in can seals. Of course, in all honesty, there is always the threat of other regulatory action but, nevertheless, it worked very well and the lead level went down considerably.

Dr. Dwyer?

DR. DWYER: I think that what Larry suggested is a very good idea.

Two other points on targeting. I don't know how it would be done, but if it could be done, it would be great. I think FDA did a campaign on hepatitis in raw shellfish and targeted people who were heavy--people who went to these raw bars and the fetal-alcohol syndrome, work

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that was done in Boston many years ago, where they focused on women who were heavy drinkers, getting them to change helped a lot.

Finally, on the effects, it is discouraging and it was wonderful to hear you speak on communications, but in a broader context, the same sorts of defeats have been experienced by the promulgators of the Ten Commandments.

DR. MILLER: Let's stop that. Johanna, you never change.

We are now going to turn to the issue of the recommendations concerning the five questions.

Response to Questions

DR. MILLER: There are some of these questions that may be easier to respond to than others in hearing the conversation of the last couple of days. I think we might do that. As I said, I was thinking yesterday of us taking the path of polling each individual member of the committee to come up with their own set of recommendations and then trying to compile them.

But, in thinking about that, it can be done and has been done, but I am not sure we have the time to give everybody a reasonable chance to pontificate, as we all are want to do, on issues of this kind.

So what I am going to try and do is to go through these issues, get your recommendations. Please keep them

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concise and to the point. I know we all feel strongly about this issue but it is important that we couch these things in terms that are useful to the agency in implementing the goal that we all seem to agree on.

I will take, if anyone doesn't specifically object, the silence of people on various issues as being agreeing with the consensus. If you disagree with it or the say the discussion is going, then just express that disagreement. But let's not pick and pick on this thing. The issue is large enough so that we don't have to pick on this in full detail.

Response to Questions 3 and 4

One of the questions on the issue is should the agency issue a fish listing as an adjunct to the advisory to clarify what is meant by a variety of fish. Is there anyone who objects to that? Let me just ask that question that way. Question No. 3.

DR. KUZMINSKI: I don't object, but, by variety of fish--

MS. DeROEVER: Excuse me. For this part of the meeting, particularly, for the transcript, we need to have comments and people identified.

DR. KUZMINSKI: Larry Kuzminski. For variety of fish, I am assuming that means eat an array of cod, tuna, salmon, et cetera.

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DR. MILLER: Right.

DR. KUZMINSKI: Not varieties of cod, different kinds of salmon.

DR. MILLER: I would think that the agency would have to define what it meant by variety if it was going to put this list together. So, in answer to it, I think, that is probably correct.

MS. HALLORAN: I would hope that, in defining it--

DR. MILLER: Give your name.

MS. HALLORAN: Jean Halloran--that they would emphasize the lower mercury varieties rather than the higher mercury varieties within the data that they have for--there are differences among varieties.

DR. MILLER: Okay.

Dr. Lee?

DR. LEE: Ken Lee. I assume variety of fish also means variety of shellfish as well.

DR. MILLER: Am I correct to assume that, when we are talking about fish, we are talking about shellfish as well?

MR. LEVITT: Yes.

DR. MILLER: I am just checking with the FDA in regard to that question.

Dr. Shannon?

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DR. SHANNON: Michael Shannon. Would the term variety of fish be limited to seafood or would it include fresh-water fish?

DR. MILLER: I think it would only refer to ocean fish. We have gone through this exercise, but I can't see how the FDA, with its mandate defined the way it is, could get into the business of fresh--there is another issue here that I want to come to and that is the question of collaboration, because it seems to me that that issue could be resolved by collaboration with the EPA and the states.

I am going to make a recommendation about that--that is not here on one of the questions--a recommendation that we consider.

Frank?

DR. BUSTA: Frank Busta. I think you are speaking of commercial fish and not ocean fish because catfish and farm-fed fish and fresh-water trout are all in the commercial system under FDA's jurisdiction. But I fully agree with you that it would be more than appropriate to include all the recreational fish if one is going to put a list together in conjunction with the other agencies.

DR. MILLER: I want to make sure I am getting everybody here. Dr. Acholonu?

DR. ACHOLONU: Acholonu. Will shellfish include clams, oysters, shrimp? I would like to know.

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DR. MILLER: Yes.

DR. ACHOLONU: Biologically, that should be unacceptable. Fish is a vertebrate organism. Clam is an invertebrate organism and can never be confused or considered as fish.

DR. MILLER: The United States Congress is not known for its biological knowledge. That is for the record.

Mr. Scholz?

MR. SCHOLZ: I was just going to say that if we looked at what some of the states did, and, obviously, I like what Wisconsin did, they have taken the step that I think you are recommending.

DR. MILLER: Right.

MR. SCHOLZ: It appears to work very well for them and very simply.

DR. DWYER: Does it work in Wisconsin? Are you pleased with it?

MR. SCHOLZ: Yes.

DR. MILLER: Dr. Hotchkiss.

DR. HOTCHKISS: I agree with this as well, but would like to emphasize that the name or nomenclature given to any particular fish is exquisitely important and I only bring up the example of tilefish for which I can't find anybody who knows what a tilefish is.

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But, apparently, by other names, it is more commonly known. It is a little discouraging to see that, while this may be taxonomically an interesting name for this particular fish, it is not the one seen in the marketplace.

DR. MILLER: That is a problem. I think we have recognized that. Johanna Dwyer has pointed out the question of species names and communication but that is not an issue we can resolve here. But, clearly, the names that are used in this thing have to be those that the public will recognize.

DR. HOTCHKISS: I am not so sure. If we are recommending defining what a variety is and, particularly, into specifics, I think it is an issue that we say is one could identify tilefish or one could identify the more common nomenclature that the public uses in tilefish. I think that is very important.

DR. MILLER: That is what I am saying for the record that the listing ought to be done in terms that the public would recognize.

Dr. McBride?

DR. McBRIDE: Since there is always going to be someone teed off because their fish wasn't mentioned, I am assuming that this list can't be all-inclusive. So I would reemphasize Jean Halloran's point but also suggest that the

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fish included by in that top-twenty-consumed varieties, maybe not exclusive of others, but include those.

DR. MILLER: Dr. Fischer?

DR. FISCHER: Fischer. I am confused on whether we have decided to add sport-caught fish or not now as Wisconsin has done. Everybody says, well, this is nice, this is good. But have we decided to follow suit with this?

DR. MILLER: This is a complicated in the sense that should FDA, or could FDA, deal in a regulatory way with recreational fish that are not within its purview of commercial fisheries.

On the other hand, what I said was that I am going to suggest, when we finish this, as an additional recommendation that we encourage the agency to enter into collaboration with the other federal agencies that have responsibility for their fish to come up with joint--so, if EPA and FDA come out with a common list, then it will include recreational fish as well. It will deal with that issue.

But if you look at Question No. 4, one of the questions is, should the 12 ounces per week per week, which they are talking about, incorporation both commercial and recreational fish. So it seems to me--let me step back, having said that and reconsidered in the last two-and-a-

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half second, I would really suggest that FDA ought to consider--if it is going to incorporate all sources of fish in the 12 ounces, it has to use recreational fish on its list as well. It does have to be consistent.

Dr. Kuzminski?

DR. KUZMINSKI: Just a comment, Sandy. I should have jumped in earlier. I think this Question 4 emanates from the discussion that we had and recognized of the confusing messages between two regulatory agencies, EPA and FDA. We have heard, also, on the need for harmonization of this message.

I don't want to beat a horse here, but just a point of view here. EPA yesterday and maybe even the day before--but yesterday, I remember that they emphasized that they give advice on this issue and don't regulate. But we do know that EPA, and I believe the public--again, an opinion--I wonder about whether the public really knows that the EPA doesn't regulate the quality of fish that comes out of fresh water.

But I wonder, also, that they do know that they regulate the quality of the fresh water. So I think, perhaps, there is a good chance of confusion at the consumer level on what is being regulated and what is being advised on when a government agency comes out with a

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statement on something like fish quality, and, don't eat these certain kinds of fish that your friends give you.

It is a tough one but I think perhaps one avenue that the agencies might explore is to have a agency responsible for regulating be the lead agency in communicating to the consumer on what the advisory is, what the action level is, whatever the issue is, and have the other agencies who have value to add to the process, certainly, advise that lead agency. In that manner, I would think some of the confusion would be taken out of the consumer's hands.

DR. MILLER: Number one, we are dealing with an advisory, in both cases. There is no regulatory proposal on the table. Second of all, I think the point of the collaboration is that they come up with a uniform, to the extent possible, advisory, maybe one which has certain things in common and is modified to suit particular local conditions.

That is a procedural question. We can't design the advisory here, certainly not in the time that we have, that's for sure. So I think that there needs to be a collaboration and we will see whether the group agrees with me on that, and it has to be one that comes up with a product when all is said and done.

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But the current attempt to put these two together is really two messages, it seems to me, that have been put together with tape, not really designed to be together.

Any other comments on this? We are recommending that the advisory clarify what is meant by a variety of fish taking into accounts the comments that have been made.

The other one, without arguing whether 12 ounces per week is an appropriate number, the question deals with whether it should include all sources of fish, both recreational and commercial. I propose that we say yes to that. I can't see how we can't say yes to that.

Okay; I am trying to get this stuff out of the way so that we can get on to the other discussion.

DR. NORDGREN: Dr. Nordgren. We are on No. 4 and I agree with it in principle, but I still have some concerns about the "12 ounces per week." I am not willing to quite sign off on either the wording or the amount at this point as a general principle.

DR. MILLER: We put the 12 ounces to the side. I think that comes under the first question. Once you have established whatever that level is, whether it should include it or not. That's why I want to separate that out because that is a different discussion.

DR. NORDGREN: With that, I agree with it.

DR. MILLER: Okay. So that is 3 and 4.

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Response to Question 1

DR. MILLER: Let's deal with No. 1 and get some recommendations. There are several questions incorporated under this first issue, and that is whether or not the agency has adequately addressed and appropriately considered all the relevant factors that bear upon the elaboration of this advisory.

If they haven't, what haven't they considered in order to reach their conclusion? This is not only the issue of what model they are using. That, as you know, is a matter of some substantial debate among a variety of groups. But what have they not taken into account?

DR. MILLER: Dr. Montville?

DR. MONTVILLE: Montville. I would really like to see, as the environmental working group suggested, a quantitative risk assessment that took into account the distributions of all the different factors and then, as new data became available, those could be plugged into that risk assessment and it could be updated.

I think working on averages is very dangerous. I think working on the 95th percentile is very dangerous

DR. RUSSELL: Rob Russell. I agree totally with what was just said. We now have 8 percent of women who are eating over the limit, as we were told yesterday. The question that I have is can we get that number down by

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restricting, and it has to do with canned tuna--by having, as part of the advisory, a restriction on canned tuna, for example, one can a week.

I need to see what the numbers show on that. Can we get that number down to only 4 percent if we gave that kind of advisory? I don't see--that data has never been presented to us and, therefore--I think that this is a very relevant part of the advisory, whether that should be included or not, and we haven't seen the data to make that judgment.

How much can we gain by putting a restriction or does it make no difference?

DR. MILLER: Dr. Aposhian?

DR. APOSHIAN: Certain, the impression I have gotten from the consumer groups is that the data has not been forthcoming from the FDA as to what data was used that they had, forgetting the Seychelles versus the Faroes, that there has been the criticism that the FDA has not been transparent--I think those were the words used--in supplying the data. And so I don't quite see how anyone can--well, it seems clear to me what the answer of the first part of this question should be, as far as I am concerned.

I would like to urge the FDA people who are all competent in experience that they be much more transparent

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and much more cooperative in getting information to anyone who wants it because, again, knowing what happened with the EPA and the arsenic problem, we have no problem whatsoever getting any data from the EPA, the water people. Everyone involved with the arsenic and the water problem gave data freely, whether it supported their point or not.

I think it would be nice to somehow make that point in the recommendation, that the FDA should be much more forthcoming with the data that is uses to make its decisions.

DR. MILLER: I am just trying to think of--all right. In addition to this question of being more forthcoming in the models, in the modeling that they did do, are there any other--Dr. Nordgren?

DR. NORDGREN: Some people have figured out my theme, I guess, in the last couple of days. Some haven't. But I am concerned on No. 5 and then how it applies to No. 1 and No. 4. I think the data that has been presented to us, the scientific studies I think have been excellent. The concerns by other agencies and consumer groups have been excellent.

But I still think, to make recommendations on the basis of average numbers that are not still being monitored, I have a major concern about that at this point in time.

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DR. MILLER: The problem is, we come down to the bottom issue, then. Do you suggest that agency takes no action?

DR. NORDGREN: No. I think the agency works with other agencies, whoever--I don't know who these are. I know your budget is limited--to make sure there is more monitoring of commercial fish.

DR. MILLER: We will come to that, but the bottom issue is that, while that data is being collected, something has to be done.

DR. NORDGREN: I am comfortable then.

DR. MILLER: Dr. Lee?

DR. LEE: I just wanted to comment that I think the FDA has earned a reputation for consumer protection that is grounded in good science. I see that the data and information that has been presented to me at this meeting and prior to this meeting to be consistent with that trend.

I don't think that there is any sequestering or withholding of data. There is just the fact that we are looking at something that is very close to baseline. We have an evolution of thinking on something that is currently being measured as we sit here in this room. The Food and Drug Administration, admirably so, is taking this information to the public before the study even concludes and recommending a behavior modification.

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So I don't get the feeling that FDA is not being forthright in sharing everything they have got with us. That isn't to say they can't do more. One suggestion that has already been raised, perhaps by Larry and others, is that they go to the industry, like the people that can tuna, and get the numbers perhaps in a single blind fashion so you don't identify any particular brand, perhaps use an intermediary like NFPA who made a statement here that says they are willing to help, and get these numbers.

I don't think I need those numbers in front of me today to say that an advisory should continue.

DR. MILLER: Just one comment. The thought also occurred to me that it might be useful to recommend that FDA publish its risk assessment in the peer-reviewed literature and, indeed, other organizations who have competing models ought to do the same and let the scientific community deal with that issue.

Does anybody disagree with that? This is really publish or perish.

Dr. Fuller?

DR. FULLER: I think I am saying almost the same thing. I just want to stress. I agree. I have no reason to doubt that FDA has not done a very diligent and put forth a very thorough investigation and review of what they

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have. I think where the difficulty has been is just that that has not been made readily available.

I am not suggesting that it isn't available but it isn't easily available. If that were the case, be it through peer review of whatever, it is then a little easier to answer the question what are the drivers, the issues that were raised a moment ago about what would be the effect of limiting the consumption of canned tuna to one can a week or whatever, to understand what the drivers are, what the bounds of those estimates that have been made on the risk assessment, all of that.

I think we could then better answer the additional questions, are factors not relevant or should additional factors be considered.

DR. MILLER: Ms. Halloran?

MS. HALLORAN: Jean Halloran. On the subject of the tunafish, I would like to suggest that the advice specifically address it simply because it is such a large part of the diet and that we just have to deal with the state of knowledge that we are in right now about tunafish. As, with everything else, it is incomplete.

DR. MILLER: Could you just hold that for a minute? When we discuss Question 2, I want to raise that question not only in the context of what fish to avoid but also what fish should we specifically--any other fish need

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to be specifically dealt with. We are still working on Question 1.

MS. HALLORAN: So you want to deal with that under No. 2. Okay.

DR. MILLER: Right. I had that in mind. I want to expand it from just simply what fish to avoid but what fish, such as tunafish--it would not necessarily be something to avoid but maybe something to limit.

MS. HALLORAN: Right. So you think that falls under No. 2

DR. MILLER: Yes; I am going to modify that.

MS. HALLORAN: As we have mentioned before, I would like to suggest that the advisory might have more prominent and specific information about young children. Rather than just have it in one line in one part of the statement, that it be, perhaps, titled Advice to Pregnant Adults and for Small Children, specify what ages we are talking about based on the toxicology; one to four, two to five. I don't know. Or one to twelve. Wisconsin does one to fifteen.

Then have specific information on what the limits translates into for a specific size of child. A 60-pound child, that would half the adult, for example.

Then, third, I would like to reiterate in this context that, because I think here we are doing factors

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they haven't considered. They haven't considered difficulties in risk communication enough and I would like to suggest the inclusion of placards at point of sale.

DR. MILLER: I'm sorry; I didn't hear.

MS. HALLORAN: I would like to suggest the inclusion of placards in point of sale as a risk-communication method.

DR. MILLER: Those are incorporated in the recommendation. Does anyone have any comment on that?

Dr. Fischer?

DR. FISCHER: Fischer. I totally agree that it should be published in the scientific literature, peer-reviewed literature, so that it can be scrutinized by peers, scientists. But I think it would be a mistake not to write a justification that would allow transparency for the public. Those are two different things. The last one is a lot harder than the first one.

But I think that should be attempted--not attempted; done, I guess.

DR. MILLER: Mr. Scholz?

MR. SCHOLZ: Brandon Scholz. I am going to concur with what Dr. Lee had said before for the most part. I also want to make the point that the retail community relies heavily on the FDA. They are our credible source.

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So if they need to justify their standards, if they need to review, then, fine; so be it.

We think that is important because of how heavily we rely on them. For us, consistency is also important and so the questions addressing--I don't know, Dr. Miller, if you would do this now or later--but the questions addressing different agencies collaborating we consider to be important.

I would also just make one more comment on the participation of the retail community in helping get the message out and participating. I don't think that you would find any hesitation on our part to do so but I guess I would need to say that it needs to be on a voluntary standard. If we get to the point of regulating placards in stores, in placement, in signage and where it becomes a complicated fight.

We are probably better able to deal with our customers in a way that we want to serve them to get them the information we want. So I would support the efforts to have the retail community be part of the delivery mechanism. But I don't know if we want to tackle the issue of whether it is regulated and mandated and how that participation comes.

DR. MILLER: I would argue that is not a decision for this group to make. That is a complicated legal

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decision. But I would also say that, in terms of making the message known, I think this group has made it abundantly clear that there are no nonrunners in this.

DR. DWYER: What did you say, Sandy?

DR. MILLER: Every possible avenue ought to be explored, whether it be placards. There is experience with the saccharine experience which mandated placards in the shops, gave some good examples of how that message got across for a while.

But I don't think anything is exempted, any possible avenue should be exempted for this. They keep saying if it is important enough, that is what you have got to do.

Dr. Shannon?

DR. SHANNON: I have a recommendation that is an extension of what Ms. Halloran said. No one, not the FDA nor the EPA nor the NAS has a risk assessment of the effects of mercury exposure to children. It is, of course, possible that a child can be--we have focused entirely on prenatal exposure with no discussion, no assessment.

It is one thing to say prudence would have children be treated as women of childbearing age. It is another to try, if the science permits, to do a risk assessment since the burning question is can a school-age child safely have a tunafish sandwich every day.

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In order to even come close to answering a question like that, there has to be a risk assessment. So I would like to see us make the recommendation that an attempt at least be made to conduct such a risk assessment on the potential effects of mercury in children.

DR. MILLER: Then, actually, for this, what factors have not been considered? That is a risk assessment in children.

DR. LEE: I sort of want to piggyback on that. I think the advisory to women of childbearing age is entirely appropriate. I would not alter that but I would just like to say that, although the focus is justifiably on the fetus and the mother, there is very scant information about men. The assumption that men are not affected or can somehow tolerate higher levels of methylmercury exposure is simply a guess.

So I would suggest that studies that look at teratogenic effects in men and those that look at chronic disease risk factors should, also, perhaps, consider collecting blood or hair mercury levels.

In practice, pregnant women often share meals with a father and data are needed on his influence, on her compliance, with the FDA advisory.

DR. MILLER: Another recommendation. Okay.

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The next question is No. 2 I would like to discuss. I would like to change that, although my colleagues at FDA might not like that, but, nevertheless, I would like to change this to deal with not only what other fish to avoid but what other fish ought to be limited, specifically tuna or pollack. I limit myself on pollack, so I am not worried about that.

Dr. Busta?

DR. BUSTA: Getting very specific on fish, I think, is a challenge and may be extremely difficult. I would like to suggest that we say something to the effect that fish consumption be from at least two of these groups or two different varieties of fish in any given week and include something to the effect that if there are extreme cases such as the Alaska case where the fish is very low in methylmercury that, in that case, it could be a singular fish.

But to emphasize that, say, no more than half of the weekly allotment come from any specific variety.

DR. MILLER: Other comments?

Yes, Dr. Shannon?

DR. SHANNON: It just seems to me that if 25 to 30 percent of the fish eaten in the U.S. is tuna that there has got to be some specific comment about tuna.

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DR. MILLER: I think was the goal of this question is probably specifically related to tuna. But the question is are there any other fish as well. But let's deal with the tuna issue. Shall we suggest that tuna be included in the avoid group? I don't think so.

I am just repeating the possibility. But, on the other hand, should no comment made be specifically about tuna and, if a comment is going to be made, what should it be?

Dr. Hotchkiss?

DR. HOTCHKISS: I will try to answer this question as straightforward as I can. I agree, the word "other species" is a surrogate for the word "tuna." It is clear that it is the most highly consumed fish in the U.S. and I don't think any of us would dispute that.

What we did not see and I think makes this difficult and important is what I raised before; what is the contribution of tuna. Simply because it is the most consumed doesn't mean that it is or is not a significant contributor to methylmercury.

Now, I did, over lunch, on my hotel bill which was already filled with a lot of errors and so I probably added to those errors, a rough calculation that said it was something like tuna comprised 20, 25 percent or so of the burden of methylmercury.

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Now, the question becomes, if that is right, which I very much doubt that it is, is that a significant enough portion of the burden to warrant a specific recommendation or not. I wouldn't want anybody to make a recommendation on the basis of my hotel-bill calculations so that makes that very, very difficult for me to answer that question without knowing specifically what is the contribution of tuna.

If the contribution of tuna is significant, is considered to be significant, then I think a recommendation that it be limited in the diet is appropriate. There is also an issue of if you take tuna out of people's diet because of its--particularly canned tuna--its very special nature, what is it replaced with and are the health risks from its replacement as bad or worse than methylmercury that might be in that tuna or, for example, reducing the protein intake during pregnant which is a significant issue in itself, or is it replaced by baloney or something else like that? That is a significant issue so it is very difficult for me to specifically answer that question without that kind of information.

DR. MILLER: Dr. Lee?

DR. LEE: Ken Lee. I agree with my colleague, Dr. Hotchkiss, on the idea of tuna should be considered. I think, almost intuitively, one can see that tuna is a

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significant source of mercury just by virtue of its huge abundance in the seafood category.

I would further say that it should not be added to a banned list as a "do not eat." I would say that there could be middle ground in that a statement such as, "consider alternatives to tuna to enhance variety" could add safety with few contraindications.

Tuna, as you see, is used as an example of a food to consume weekly by pregnant women in the state literature from Wisconsin in the Women's Guide to Eating Fish. I don't think this was intentional but it gave an inadvertent impression that tuna has been checked out and it is safer than other fish.

So, unless we go on record in having a specific recommendation here, this kind of inadvertent translation in consumer literature is going to continue to occur.

DR. MILLER: Dr. Aposhian.

DR. APOSHIAN: Again, I want you to consider the fact, as Dr. Shannon has already pointed out, that children are not just small adults, that on a per-kilogram basis, no data has been given to us by the FDA as far as amount of methylmercury per kilogram and the child's sensitivity to it.

There is an old rule in toxicology; the dose determines the poison. I certainly am not in favor of

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abandoning tuna. Neither am I in favor of saying it is something that should be avoided. But I think the data, a warning of some kind, should be given, especially for young children who--because I remember when I was a boy, tunafish sandwiches were the easiest thing to take to school to lunch before school lunches became available by the government.

I think that it is necessary to bring this to people's attention. Just because enough data is not available does not necessarily mean we should ignore the problem. I would just urge some kind of advisory that includes tuna.

At present, as I understand it, the advisory does not include tuna.

DR. MILLER: I also haven't heard any information on this from any of the groups that spoke to us. There is nothing on the exposure in a per-kilogram basis.

Dr. Bolger?

DR. BOLGER: Mike Bolger. I don't recall whether Susan Schober mentioned this in her presentation but the NHANES is showing us that the body burden--so I am talking about blood now--in children is about three-fold lower than their mothers. So the NHANES data is showing, from a blood level, body-burden, perspective that children have lower blood levels than their mothers.

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DR. APOSHIAN: But that says nothing about the toxicity.

DR. BOLGER: Oh, no. I am just talking about body burden, because you did say something about relative consumption exposure. I am just saying, if you look at blood, it says that the children have lower levels than their mothers.

DR. SHANNON: That is deceptive, though; right? Was that one through fifteen? What was the age group?

DR. BOLGER: I don't recall the age group. One to five?

DR. SHANNON: That is not an age group eating tuna.

DR. MILLER: Dr. Shannon, did you have another comment? Dr. Dwyer?

DR. DWYER: I was just going to agree with Dr. Lee. It is always good to go to the Midwest for common sense. Wisconsin has a lot that we need to consider.

DR. MILLER: Dr. Montville?

DR. MONTVILLE: Montville. Again, I think using aggregates for mercury levels in tuna in children can take us to a place that we don't want to go. In the absence of knowing that it is safe, I think we have an obligation to the public to say, "this is something you might want to limit."

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Clearly, it is not the high concentration of the "don't eat," but, because of the consumption rate, there is, I think, more potential risk than the other fish. So I think tuna is a little bit in a class by itself.

DR. MILLER: Larry?

DR. KUZMINSKI: Larry Kuzminski. I think we need to be careful on the answer to No. 2 to avoid getting into the good-food, bad-food, good-fish, bad-fish, position. I think the answer to No. 2 should be data-driven. I sense that there is more data available to the agency if it were to ask on what the mercury levels are in canned tuna.

I sense that there have been a couple of other suggestions on risk models to be done on tuna consumption in children and should those data generate a particular answer to the agency, then I think that is the position the agency should take in terms of being data-driven to formulate a position.

DR. MILLER: Dr. Dickinson?

DR. DICKINSON: I would agree with that. I think the evidence that we have available to us now, based on the NHANES data and other data that has been presented these last couple of days doesn't suggest that tuna contributes in any way except as part of the overall background. I mean, it is there but there are numerous other fish on FDA's list of mercury levels that have similar levels.

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I recognize the importance of the cumulative content, but I agree with the point that we should be driven by what the evidence will show us from NHANES eventually is responsible for the elevated mercury levels. And I don't think we have that now.

DR. MILLER: Dr. McBride?

DR. McBRIDE: Margaret McBride. Another point I find difficult with the tuna data is, though we know that tuna is eaten as, perhaps, the top fish eaten, we are given an aggregate or a mean of the methylmercury content but, if I remember hearing some things correctly, and correct me if I am wrong, the light tuna versus white tuna is at the lower end of that range and I believe is also cheaper.

So the question is not really the average of cans off the shelf times the quantity eaten as far as the burden to society, but it is much more complicated than that. It is how much at each end of the spectrum, et cetera. So it is a difficult question and, in that spectrum, include some that are quite a bit--some cans, I am assuming, that are quite a bit lower than the average so we almost do the reverse of our intent if we say to those that happen to be the good tuna eaters limit.

DR. MILLER: Ms. Halloran?

MS. HALLORAN: It is useful, though, to look at what Wisconsin has done where they gave, as an example of

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weekly fish consumption, one can of light tuna and one serving of something else. I think if it was presented as an example of how you interpret this advice, I think that could be very helpful to people and get the idea across without having the bad connotations that we are concerned about.

DR. MILLER: Dr. Hotchkiss?

DR. HOTCHKISS: In my view, the call for more data is sorely misguided. We know what the methylmercury content of tuna is. We know the range. We know the standard deviation. There is a lot of information out there. We probably could regionalize that information and we know a lot about it.

If is very simple, through a number of things, the TAS system, and so forth, in selecting different populations groups and finding out as tuna casserole, tuna sandwich, whatever you want, what they are consuming.

So we can go to the 95th percentile tuna consumer of a specific kind of tuna if we like and we can say how much tuna they are getting. We can pick a number for what the concentration, or we can do a Monte Carlo kind of analysis and go all across this thing. It is not a matter of getting more data.

It is a matter of taking some of those exercises and gaining information from those exercises and then

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making a risk-management decision based on the outcome of those kinds of things. My point is that, while we have this base information, what we don't have is the scenario analysis of that information to tell us tuna is a minor contributor to a child-bearing-age women's burden of methylmercury or it is a major source or, more likely, it is something in between.

That is the kind of analysis of the data we already have that we need.

DR. MILLER: Dr. Shannon?

DR. SHANNON: I just wanted to agree with what Dr. Kuzminski said. It is sad but true that I don't think that we have sufficient data here today to kind of give FDA guidance on what to say about tuna because the two big things that we are missing are, one, the risk assessment on postnatal exposure, for example, to school-age children and, two, the kind of risk cup analysis that can only be done when FDA and EPA get together and try to get a sense of what average exposure to all types of fish are for the populations we are concerned about so that you really do have a sense--I think, only then, can you talk about where tuna fits in the grand scheme of things and really make a risk cup that you feel comfortable with.

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Absent those two bits of data, I would have no idea what to suggest to FDA that the tuna recommendation say.

DR. MILLER: Sitting here thinking about this, I am reluctant to leave it blank. I am concerned about a particularly susceptible population although there are some areas where children are less sensitive than adults. But I don't think that is the case for methylmercury.

But what I would suggest that you consider is the possibility if there is a belief that there is insufficient data to come to a decision concerning--I won't say avoidance, but limitation or whatever, that we might consider specifically recommending to the agency that they do these analyses on a priority basis and make the decision once the data is in. But to focus this on the tuna specifically rather than on all fish, we would establish a priority.

DR. SHANNON: I agree.

Dr. Friedman?

DR. FRIEDMAN: My comment is not just for this question. It is more general. Can I bring up something that is more general regarding the advisory?

DR. MILLER: Let me just get a feeling of the committee on what I just said and then we will go on to your question.

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DR. FRIEDMAN: Okay.

DR. MILLER: Dr. Aposhian?

DR. APOSHIAN: It bothers me. Essentially, you are saying that we don't know whether methylmercury--we don't know that the amount of tunafish that children eat is enough to cause them damage; isn't that correct?

DR. MILLER: Yes; I think that is correct.

DR. APOSHIAN: Then the next question is are we willing to just ignore the situation for a period of time that we don't know how long it is going to be before FDA goes through the risk analysis, gives us advice and eventually publishes it.

I think that there is substantial evidence that children are harmed by methylmercury. I think there is substantial evidence that tunafish is one of the major fish consumed by people, especially poor people, and by children. I think it would be a mistake to ignore this. I would rather take the position that let's issue some sort of cautionary advisory that can be revised rather than ignoring it.

Again, the Wisconsin example, I think, is excellent. I think you all have this. It is a Safe Eating Guideline for Women who are Pregnant, Planning to be Pregnant, or Breast-Feeding for Children under Age 15. It goes through the tunafish problem.

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It seems to me that it would be a mistake just to wait. We can always change a decision. But I would much rather have that decision geared towards extra safety rather than just being ignored for a period of time.

DR. MILLER: So what has been recommended, let me take that, and put another idea on the table is that we recommend some kind of cautionary statement, certainly not an avoidance statement and not necessarily one that is a specific limitation but a cautionary statement and, at the same time, recommending to the agency that they make doing the analysis to get the data a priority issue.

Dr. Montville?

DR. MONTVILLE: I have to modify my previous position a little because I have been thinking what has been driving the tuna issue is not the concentration but the frequency of consumption. So if we tell people to limit that and they substitute it with some other middling amount fish, it is not going to decrease the mercury burden at all.

So I think, going back to what Dr. Busta originally said is that people should be encouraged to eat a variety of fish or to be made known that "you should eat something other than just tuna all the time." It could be put in a positive light and probably do just as much good as maybe badmouthing tuna.

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DR. MILLER: A positive cautionary statement.

DR. MONTVILLE: Yes.

DR. MILLER: Dr. Friedman, I haven't forgotten you. I am just trying to get this issue out of the way.

Dr. Hotchkiss?

DR. HOTCHKISS: Joe Hotckiss. I would certainly agree the position that we should be cautionary, but you also have to remember that every time you change someone's diet, you run other risks as well. For example, one might substitute for canned tuna another fish in the diet. If you look, under Tab 22, the list, many of the most popular fish--for example, halibut--has a higher concentration of methylmercury than tuna.

So one might say, "I should limit my tuna intake. I like mild fish. I am going to choose halibut." The end result of that is that you have given a greater methylmercury burden. Or I might substitute, because of the cost, baloney or peanut butter or other kinds of things to my diet. Remember, we are talking primarily about pregnant people for which high-quality protein has some benefit, I believe.

So, in the absence of--I could go along with all this if someone said to me, "Listen; tuna is 40 percent of a woman's burden of methylmercury during pregnancy." Then

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I could say, "Gee; that is something we ought to do something about."

I haven't heard that number. If we had some specific kinds of risks over that, then this decision would be easier. But, in light of that, I don't think we can risk making the wrong decision telling people to substitute a higher mercury-content fish or baloney or other inexpensive food into their diet.

I would agree that prudent course for me seems to be to strongly recommend to the agency with due haste that they make those kinds of calculations and decide, for different populations, what the methylmercury burden is due to tunafish and publicize that information.

DR. MILLER: Dr. Aposhian.

DR. APOSHIAN: I urge you all to pick up what you were handed by Wisconsin. We all believe--or I have always believe, even though I am not a citizen of Wisconsin that the state has been very progressive in its health endeavors. It says, "Weekly. One meal per week of canned light tuna (6-ounce can equals one meal) and," and the and is in bold, "and one meal per week of either blue fish, sunfish, black crappie, white crappie, yellow perch, bullheads or any commercial fish, fish you buy in a store or restaurant."

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It seems to me that that doesn't say you should not eat canned tunafish. It seems to me that it gives you other choices. I don't know anyone on the committee who would want to ban any of these fishes because we realize that it is necessary to have a useful diet containing the omega-3 and other fatty acids.

Again, I would hate to see children put at risk just because we don't have all the data yet when there is a lot of data, both animal and human data, that methylmercury can do harm.

DR. MILLER: Dr. McBride? It is on this issue; right?

DR. McBRIDE: Yes. There is also that double asterisk there on the Wisconsin handout that says if you don't eat anything but tunafish, two 6-ounce meals a week is okay. That is a problem. The big tunafish eaters don't eat anything else but tunafish and they are not going to go out and get crappie and yellow perch and cook it.

DR. MILLER: Mr. Scholz?

MR. SCHOLZ: Just not to disparage the fish and to make a minor correction, it is "croppie."

DR. MILLER: Dr. Lee?

DR. LEE: I think we are all pretty much pretty consistent and can achieve all things. If we ask FDA to study these numbers and, in due haste, make a

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recommendation, that, indeed, is desirable. We all know the lightning speed at which government works and it might be to our best interest to say something in the interim or put a time frame on that response.

I would go back and suggest that a statement such as, "Consider alternatives to tuna to enhance variety be incorporated in these recommendations." It is benign enough that we are not banning the substance but we are concerned about the large potential contribution to the burden.

DR. MILLER: Dr. Kuzminski?

DR. KUZMINSKI: I go back to a concern that I thought I heard relatively commonly around the table earlier on, mixed messages and the number of message. I guess I am sort of in the camp of--I hear the comment on that we know what the levels are. I go back to Tab 22 and look at the total number of samples that have been run for tuna and canned tuna, just focussing on canned tuna.

If there is more data truly available, hastily available, in quality fashion, then I guess I am for ratcheting up the effort to get that data, putting a time frame on the result like the end of the calendar year, and go forward with whatever message the data drives you at that point in time.

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DR. MILLER: There is another possible solution. I thought I had it before. As Dr. Kuzminski said, there is a period of time during which these documents have to get drafted. The process required by law for the agency to develop these kinds of activities is simply time consuming. It can't be done overnight.

We can, and have expressed, I think, in the record of this discussion, our concern for children. What we disagree with is what action to--we all agree that the agency should take and collect the available information, do the appropriate risk assessment for children, et cetera, et cetera, et cetera. We have already stated that and I think that is something we all agree on.

But I would suggest also that, instead of just saying they should add a precautionary statement, a prudent statement to it, say they should be working on the development of an appropriate statement suggesting limitation of tuna consumption as part of a mixed--while this process is going on. And then, at the time, whether the time comes to implement it or not, by that time, I think the science part of this will have been developed and the agency can make a decision based on whatever the science is going to be.

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DR. APOSHIAN: I am not quite certain I understand. Are you saying that we are going to ask for a cautionary statement?

DR. MILLER: We are going to say the agency should be working on an appropriate positive statement that will also recommend limitation in consumption of canned tuna and, at the same time, encouraging eating a greater variety of fish.

DR. APOSHIAN: My concern, knowing how my university functions and most government agencies function is are we going to put a time limit on when that is going to appear?

DR. MILLER: There is a period of time that it will take the agency to do this under law. It has got to follow certain process for any action it takes up to and including notice and comment and so on to get people's responses back.

I am saying that they ought to be working on this and the science at the same time. I assure you that the science will be done long before the statement will be done.

DR. APOSHIAN: That takes care of the children. I don't think we have yet addressed the pregnant women who will eat a number of cans of tuna not knowing about this. Again, the Wisconsin statement--

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DR. MILLER: What I am proposing is that the agency work on a statement like that in the Wisconsin--

DR. APOSHIAN: For children and pregnant women.

DR. MILLER: For children and pregnant women and, at the same time, do the science and hopefully, and probably will happen, the science will be available before that will be available and then, at that point, make a decision to see if the science supports it.

I am out of ideas.

[Echoes of support.]

DR. MILLER: Dr. Friedman, finally?

DR. FRIEDMAN: I am looking here at the advisory, the FDA advisory. We have been talking here over the three days about the importance of changing behavior. This is the purpose of the whole thing. It starts with a statement about the fact that seafood can be an important part of a balanced diet. However, some fish contain high levels that can harm an unborn child's developing nervous system.

I don't know who is the audience, exactly, of this. I don't know how many young women know exactly what we mean here by developing nervous system. I am not sure that we know what we mean by developing nervous system. I think there needs to be more specificity.

If I am a pregnant women, I want to know what it means if I eat a little more tunafish. Is my child going

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to be retarded because of it? Is the child going to have severe motor dysfunction? Is the child going to lose one point of I.Q.? I think we need more specificity here. Otherwise, why would people follow the suggestions?

DR. MILLER: What you are saying is that the advisory should be more specific in outcome.

DR. FRIEDMAN: If this was a consent form--suppose we were an IRB here and someone wanted to do a research project, wouldn't we need to have more specificity in terms of what we are looking for and what we are expecting to find? We would. We wouldn't be able to get our project done.

DR. MILLER: I see nothing wrong in making the statement that it be suggested to the agency to consider this. But remember, again, this is part of a conflict between simplicity and short messages and more detailed messages. Consent forms are not exactly the most succinct messages I have ever seen.

DR. FRIEDMAN: This was just an analogy. The point is that the public--we are asking the public to comply. Why should I comply? First of all, I may think that, by eating a little every day tunafish my child will be deformed or will be retarded which is very alarming and incorrect. This is at the extreme.

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I would certainly want to know more detail than the vague notion of neurological deficit.

DR. MILLER: Any comments? It is a conundrum because of the desire to be more precise and the difficulty of doing that within the confines of a short message that people will actually read. It is the old labeling problem about how much can you get on a 3-ounce tuna can.

DR. FRIEDMAN: I just thought I will mention it.

DR. MILLER: No, no. It is on the record. I want everybody to understand, anything you say is on the record. The agency will review all of this. Even so some of these things are not issues that we have agreed on as a group, they will be considered by the agency as part of their--

DR. MILLER: Dr. Fuller?

DR. FULLER: Just sort of a comment on that one and that is I also don't want to get into the business of trying to wordsmith the advisory to death. I think that one of the things we have been hearing around the table is that when you are doing risk communication, that balance of when you have got a complex issue of how you get your message across and don't confuse too many messages in that delivery, et cetera, I think there is benefit and, perhaps, something that could be given some consideration, too, is just the old "for additional information."

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I am not certain that, in an advisory where you are trying to get a complex message fairly simply across, you can get into a lot of detail, but I think you can direct, not necessarily just to your local health agency, but providing, perhaps, in that small print, additional specifics.

It may be in here; the website, which is easily navigable and gets you to additional detail, whether it is for the risk assessment or information on the various different types of fish, et cetera.

DR. MILLER: What you are saying, in essence, and I think everyone would agree, that the message that is distributed through the various channels that will have to be used for this, whether it be professional channels or whatever, ought to be designed specifically for that channel. The same message isn't necessarily the one I would use for physicians or for other groups, for the media, et cetera.

Dr. Scherer?

DR. SCHERER: I would just add my two cents. It seems to me that the real issue here is simply a recommendation that any message that is produced should be pretested on the audience so that we understand what they know and learn from it.

DR. MILLER: On the recipients; yes.

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DR. SCHERER: Yes. If it is for physicians, then physicians should actually look at it and describe what is it they are getting--

DR. MILLER: An excellent suggestion.

DR. APOSHIAN: Can we, perhaps, even recommend that the FDA have a risk communicator like Dr. Scherer put on this problem with them? Is that out of our jurisdiction?

DR. MILLER: No, no. We can spend their money.

DR. APOSHIAN: Money is money but, still, I think many of us are learning a great deal about risk communication. I don't know how much the FDA knows about but it certainly could not do any harm to have Dr. Scherer--that we recommend that Dr. Scherer or someone with his qualifications be an advisor to the group at the FDA who is going to come up with this advisory.

DR. APOSHIAN: I think that perhaps what we ought to say is that, recognizing FDA has its own risk communicators, that, in order for this to be done properly, all the most experienced individuals involved in these areas ought to be consulted. It is really important enough a problem, and that is what I keep on saying, that it really deserves attention as a primary priority for the agency, for the agencies, I think I can say.

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It has been important but I have no idea where this has been a priority of the FDA. But I think this group indicating how important it is would be helpful in establishing this priority.

DR. HOTCHKISS: Point of order. I would like to see us talk about Question 5. The real risk to me is another night in this wonderful hotel.

DR. MILLER: I am not going to comment.

DR. DWYER: I have one sentence and that is if this isn't--whatever the final upshot of this advisory is, perhaps the agency and the department needs to consider incorporating this into Healthy People 2010, the interim review in 2005. I believe they changed the objectives a little bit then, and that would bring all six Public Health Service sister agencies together in one happy family.

DR. MILLER: Thank you.

I think we have reached a consensus. What exactly our consensus is, we will find out when we read the record. Nevertheless, I would like to turn to the last question.

DR. ACHOLONU: I just have one. I know we have been spending time talking about the tuna situation. There is another aspect of Question No. 2 that I don't think we have addressed. I would like to recommend to FDA that they should expand the list of different fish species that

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should be avoided by pregnant women if the information becomes available to FDA.

The reason why I say this is I have read some publications making a list of some species of fish whose mercury content exceed 1 part per million. An example of that is redfish. Another one is what they call the black grouper. And there are others. Should we include, in our recommendation, that the FDA increases or expands the list as more information becomes available.

DR. MILLER: Any comments? If not, I think it is a perfectly reasonable thing to do.

DR. ACHOLONU: Thank you, sir.

Response to Question 5

DR. MILLER: Let's move on, so that Dr. Hotchkiss can go home happy, to the final question about should the agency increase its monitoring of methylmercury in commercial fish to keep its advice current.

I would ask the question differently. Does anyone disagree with that? Dr. Nordgren?

DR. NORDGREN: Dr. Nordgren, again. I don't disagree. I certainly strongly agree with this monitoring being done. I don't understand the budgetary constraints of the various organizations involved. I would not want this done at the expense of some of the things, maybe. But I think this needs to be done.

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I don't think it can be our decision to say who does this. But, to me, it is extremely important that this part be done. But I worry about the FDA. I know there are limited dollars, healthcare dollars. I don't think I can be in a position to prioritize--I hate that word--but put in a list of what are very important things. I think somebody needs to do this.

DR. MILLER: That's correct. But I think it is important that, if we recognize that it is important, we ought to make that recommendation.

DR. NORDGREN: I recommend this as being extremely important.

DR. MILLER: Dr. Hotchkiss?

DR. HOTCHKISS: Joe Hotchkiss. My concern about this is that, over the last three days, we have heard a number of individuals call for increased monitoring by FDA. In my view, we know pretty much what the methylmercury situation is in fish. We have an ongoing marketbasket which really, while limited in size, is intended to find out what, not only for methylmercury, but other toxicants in the data.

I would be very disappointed to force FDA into spending limited resources to find out what they already know. There are other kinds of research questions, I think, that if FDA wanted to dedicate more money in this

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area, they could gain more from. For example, a broader sampling of biomarkers of methylmercury exposure, hair, relatively simple research to further test in more detail, test different messages in different groups.

There are things that need to have money thrown at them and to be done by FDA, but to increase its sampling and monitoring program I don't think will bias very much. My concern is that those calls for--there is a tendency, even in the agency when I was there--there was a saying that if you sample a problem enough, it will go away.

I would hate to see that happen in this case. There are much, much better ways to spend resources.

DR. MILLER: Dr. McBride?

DR. McBRIDE: Margaret McBride. Actually, that was similar to what I was going to say. Maybe we need to expand the statement to say monitoring of not just fish but of this young-children group, for instance, that we don't seem to know, the five to twelve or the five to fifteen and that sort of thing.

DR. MILLER: I was going to ask that question, whether the monitoring should be expanded to incorporate concentration of human biomarkers or in addition to whatever was done in fish, itself. It is true you can sample things to death but I think, on the other hand, I am

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not sure that we really have a enough data to really be able to determine with some accuracy what the limits are.

I think that needs to be done. I think there are experts at the agency who could deal with this. They are doing this all the time. We throw a lot of money at pesticides. In fact, a lot of that money is wasted. We know what the pesticide concentrations are. But it is done because Congress told the agency it had to do it.

Dr. Shannon?

DR. SHANNON: I was going to disagree with Dr. Hotchkiss and agree with what you just said. I don't think monitoring has been adequate. When I look at, over the course of the three days, that measurements of tuna are based on only a couple of hundred samples, and that is supposed to be an estimate of the population of tuna, I find that woefully inadequate.

Now, that doesn't necessarily mean that the FDA needs to enhance its own monitoring. If someone else is doing that and provides that data to FDA, then that is a reasonable alternative. But I would completely disagree if anyone were to suggest that doing 200 to 300 samples is adequate.

DR. MILLER: Ms. Halloran?

MS. HALLORAN: I agree with Dr. Shannon. When we have in Table 3 certain species where they have done

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exactly four samples, trout, sea water, samples, and one of those was 1.19, there is a significant possibility that, if they did a hundred samples, or even fifty, that that could be a candidate for the "do not eat" list.

We don't know. We really don't know. But when one of four is 1.9, that is a serious concern. So I think there are some. If you wanted to say that monitoring of commercial fish where data is lacking or something, because, obviously, some categories are much better than others. But these, where the data is so scanty, it does seem to need more monitoring.

DR. MILLER: Perhaps it might be useful to modify by suggesting that the agency increase its monitoring of commercial fish in collaboration with the industry and other interested groups, something like that.

DR. MILLER: Dr. Lee?

DR. LEE: Ken Lee. I find this statement to be a little too restrictive in that I think we have to trust our regulators within the government to monitor what makes most sense scientifically in terms of information needs.

So I would suggest that the agency should increase its monitoring of methylmercury in order to keep its advice current. Let's not forget that we are all assuming that seafood is the only significant dietary or

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environmental source of methylmercury. I am not quite so sure that is the only place it is coming from.

We saw some evidence of individuals that didn't eat any seafood that had appreciable content in tissue. I would like to allow the scientists to explore what needs to be explored.

DR. MILLER: Dr. Fischer?

DR. FISCHER: Fischer. I just think a more general statement, say, "The agency should increase its collection of information on methylmercury exposure." They could do the monitoring themselves or they could collect the information from the states or other places, industry. Just give them the idea that they have got to increase the information base on exposure.

DR. MILLER: Did you incorporate in that exposure the statement, human biomarkers, hair, et cetera?

DR. FISCHER: Yes.

DR. MILLER: Do we all understand what he is saying? Okay.

DR. MILLER: Dr. Kuzminski?

DR. KUZMINSKI: If the statement were also to include a highlighting of presence in pregnant women, I think that would be an important addition to make. The comment was made during Dr. Lockwood's presentation, I think it was yesterday, on the possible role that the OB-

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GYNs could play in the enhancement of the knowledge base of the mercury content of pregnant.

I think that is an avenue that the agency might want to explore.

DR. DWYER: I agree with both of those statements.

DR. MILLER: Dr. Shannon?

DR. SHANNON: I guess I just want to ask, the issue of adding the recommendation on biomonitoring. Is that because we feel that NHANES is inadequate or it should be in addition to or supplemented? Isn't that the purpose of NHANES?

DR. MILLER: I think the question is does the sampling of NHANES really represent a population distribution. One of the questions the agencies might--I am just trying to indicate how this could be responded to--should we have more geographical data which NHANES doesn't give you? There are a lot of questions about that.

It may not be any and it may be, if it is serious enough, that the federal agencies, not just FDA, could enter in the kind of thing that are been done in some of the states that we--

DR. SHANNON: Is there a precedent for that? Has the FDA ever done biomonitoring, done population biomonitoring?

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DR. MILLER: I don't know. I can't think of it. I don't think that has ever been done. That doesn't mean it can't.

DR. SHANNON: I agree.

DR. MILLER: I am a firm believer in tradition but only when it suits our purpose.

Dr. McBride?

DR. McBRIDE: Margaret McBride. I am not sure when the right time to bring this up, and we have touched on it, but we have the problem of trying to get a simple message out when there are pockets of the population that have either much less, as in Alaska, potentially, or much more as in some of the coastal areas, say, Mobile, exposure. We haven't really mentioned that.

Somehow, we don't want to get in the way of firstly, no harm. We don't want to get in the way of either stronger or less strong advice that is locally appropriate. I am just raising that as an issue. I don't know quite how to address it unless, possibly, if we go to this kind of form, it can be clear.

DR. MILLER: I think we have already said that the advisory ought to be put together in collaboration with other federal agencies and the states. I could visualize--I don't know if this would ever work--a statement that was basically formatted in a similar way and that was a general

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statement to begin with and then individual statements within the various--attached to it. I don't know if that would work.

But I think this is one of those issues that requires really close collaboration among agencies and among agencies in the states. There are others like that, food-intoxication, food-safety, issues, increasing demand that the states and the federal agencies interact more closely in order to keep control of contamination of food stuffs and so on.

I think this is one of those issues where it could work very well, indeed.

Are there any other--I don't believe this. We actually finished on the moment that we thought we were going to finish, we hoped we were going to finish.

DR. FISCHER: I have a point of information. I feel I must say, or tell you, that Dr. Henry Anderson from the State of Wisconsin informed me that this Wisconsin advisory, which we all admire, was stolen from another state. I think it happens to be Maine, if I am remembering correctly. So just so Wisconsin doesn't get in too much trouble claiming that this is theirs.

DR. MILLER: If there are no other comments, let me truly thank you all. This has been an excellent consultation. I think we have given the agency some very,

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very useful advice. I am looking forward to monitoring their progress on this in the future.

This part of the discussion will be transcribed. The whole meeting will be transcribed, but each of you will be provided a copy of this part of the discussion, for your information.

Thank you all very much.

[Whereupon, at 3:30 p.m., the meeting was adjourned.]

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