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ATDEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR FOOD SAFETY AND APPLIED NUTRITION

FOOD ADVISORY COMMITTEE

METHYLMERCURY

Wednesday July 24, 2002

8:30 a.m.

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Dr. Elizabeth Southerland
Dr. Henry Anderson
Dr. John Middaugh
Dr. Charles Lockwood
Dr. Diane Zuckerman
Mr. Richard Wiles
Mr. Michael Bender
Mr. Bob Collette

C O N T E N T S

P R O C E E D I N G S

DR. MILLER: Let me welcome you to the second day. We have a lot of speakers and we need to make certain that everybody has enough time for their presentation. I will remind you when you have five minutes left for your presentation, and then when the time is up I will remind you of that and, if necessary, we will wrestle for the microphone.

We are destroying more trees again this morning; the pile of papers that you have been given is increasing logorithmically. In view of the discussion we had yesterday about what was a tile fish and what was a mackerel, and so on, we have some pictures of both fish so we know what we are talking about. We don't have quite enough copies for everybody and you will have to share them, but I think that will answer the question, yes, Virginia, there is a tile fish.

Our first speaker this morning is from the EPA, Dr. Elizabeth Southerland. Dr. Southerland?

Environmental Protection Agency

[Slide]

DR. SOUTHERLAND: In the Office of Water at EPA we have a program that gives technical assistance to state

and tribal health departments to help them put together fish consumption advisories, if they choose to do so.

[Slide]

Our program provides technical assistance, and we do a number of things. First of all, we have a national guidance that talks about what types of species you should sample; what analytical methods are available to give low detection limits in those species that are sampled. We have a risk assessment document that talks about once you get those concentrations in the fish, how would you calculate the number of meals that you want to recommend a person make of those species. Then, we have a risk management guidance and we also have a risk communication guidance, and I will talk about that a little bit later.

We also have a national database. Since 1993 the states have voluntarily been giving us each year data of their fish consumption advisory. So, if you go on our web site you can see all the fish consumption advisories that consist of state health protection throughout the United States and that, again, has been occurring since 1993.

We also have national conferences and workshops. Every year the states meet with us in a fish forum. Generally we do this with the American Fishery Society. This year it will be in October, in Burlington, Vermont when the states meet with us. We will be talking this year

about emerging contaminants, some new pollutants that have started to show up in fish, and we will also be talking, of course, as always about the benefits of eating fish.

We also have grants for sampling and analysis. In some cases a state will have a suspicion that there is some contamination in their fish. They just need a little bit of seed money from us to actually go out and measure to see if, in fact, there is a contamination problem. Whenever we can, we try to provide grants to states for them to do that.

We also do special studies. We have been working on a random stratified sampling of all the lakes in the country. It is a big four-year study, multi-million dollar, in which we are randomly sampling lakes of all different sizes around the country and measuring them for over a hundred different contaminants. It is not just the old banned chemicals that we have already been concerned about, but it is a lot of new chemicals, new pesticides that are currently being used and we want to check and see if there are some emerging pollutants that currently we are not sampling for on a regular basis. So, that is one of the special studies we are doing.

Finally, a number of times states, particularly in inter-state waters where there is a disagreement between states sharing a body of water over what kind of fish

consumption advice they want to handle, they will often call us and we will provide technical assistance to the involved states.

[Slide]

I have done this just for lake acres. A similar pattern, however, would be shown for rivers. Across the X axis is the number of lake acres under advisory, and this is in millions of acres. Then, along the Y axis we have the five most frequently detected pollutants. Again, if you look at our web site you will see that state health departments have set fish consumption advisories for 39 different pollutants. These, however, are the five most frequent. Dioxin doesn't show on the graph. There are 75 fish consumption advisories in the country for dioxin. It is just that in terms of millions of lake acres it doesn't quite show on the scale.

We have been measuring these advisories since 1993. The states have been giving us this data. So, you will see that the real trend in terms of increase in advisories is in mercury. Again, we don't think that that is an indication that there is some new contamination source of mercury, it is that the states have more and more over the years begun to monitor their fish for mercury concentrations. So, that is why you will see that that is now the most prevalent cause of fish consumption advisories

put out by the state health departments, and it has been increasing, much more so than the other pollutants which have pretty much stayed about the same.

[Slide]

This is a really busy slide and I ask you to please look at the handouts. We have them at the front table, if you haven't already picked one up. This map shows several things and I will try to walk you through it and then we can talk more about it in the questions and answers, if you want.

The states that are in white, they are ones that do not have any fish consumption advisories at all. It is mostly in the West and Alaska and Hawaii. The ones that are in pink, varying shades of pink, or striped pink, or red are states that do have fish consumption advisories. They may have statewide advisories that say all the freshwater fish in this country are under some kind of mercury advisory, or they may point out individual water bodies for fish consumption advisories. It is not necessarily all species of fish; it may be selected species of fish. It may not be all waters; it may be certain waters. So, it varies state by state but we are trying to show this to you on a national basis.

The reason you have that blue line around the southeastern Atlantic coast and all of the Gulf of Mexico

is that the states that border that coastline all have coastline advisories for mercury for a number of species of fish. So, that is why you will see the blue there.

The other thing of interest here is that there is a little square in 11 of these states, and many of them are on the northeastern side so you can't even see it in the little tiny state itself but it will be written next to the state name. But it is a total of 11 states which have given their public advice on commercial species as well as on recreational species. The reason they did this is because they realize people do not only eat fish that they catch themselves, but they also go to the store and to the restaurant and they eat commercial fish too. So, these 11 states are giving advice to their public on eating commercial species of fish as well as recreational species. Nine of the 11 states that issue this commercial advice include tuna in their recommendations because so much of the diet that many people eat of fish are tuna fish sandwiches.

We used these states as an example in trying to do our national recreational fish advisory. So, when I talk about that at the end of my presentation you will see that we included the FDA advice in with our recreational fish advisory to try to keep down confusion where we are seeing some difference for recreational fish than FDA is

saying for commercial fish. So, we use the example of these 11 states as a model to follow, and I will discuss that at the end.

[Slide]

I know we went over this ad infinitum yesterday, but the reason I am repeating it now is as a reminder of what we use. EPA uses the RfD that the National Academy of Sciences recommended in July of 2000, and that is the 0.1 ug/kg body weight per day. ATSDR has a different number and FDA has yet again a different number. The reason I am going back through this is for the next slide.

[Slide]

If you look at the RfD that the states use for setting their mercury fish consumption advisories, it varies by the state. Again, if you look at the top graph, I think it adds up to 38 or 39 states that give advice that they call out just for adults. That means they are not differentiating women from men; they are just saying adults. Of those, 25 of the states that give advice for adults will use the 0.3, which is the ATSDR number. Seven of them use the National Academy of Sciences EPA number of 0.2 and then there are smaller numbers using RfDs on either side of the scale.

If you drop down to the second graph, this is the number of states that are giving specific advice for women

and children. These states generally, 23 of them, use the 0.1 or the EPA RfD. There are four of them that use the ATSDR number and then a few that use other numbers on here.

So, when you drop down to women and children, it is generally the 0.1 that is being used to give their fish consumption advice. It turns out that there is a total of 16 states who give both kinds of advice and use different RfDs depending on what public they are trying to look at. So, we call that a two-tiered advisory. What those 16 states do, they use the 0.3 RfD to give advice for women who do not wish to have children or are too old to and for men. That would be the adults. Then, for women of childbearing age and children they use the 0.1.

So, that is generally what we would call two-tiered advice. All the other states that give advice use a consistent RfD for adults versus women and children. There is a lot of information there and, again, it is state by state so we can talk about that in questions and answers also.

[Slide]

When I talked about the national guidance that EPA puts out, again, we update this guidance about every two years just to keep current with the science. Again, the sampling information will talk about what species and what kind of analytical methods you should use to get as

low as possible detection limits. Our risk assessment guidance is the type of equation that we would follow and that we use for our national recreational advisory. It is basically set up to calculate allowable meals or recommended meals based on the fish concentration that you have.

Again, we have risk management and risk communication guidance. The risk communication guidance that we have has some really innovative things that several of the states have come up with on getting the word out very effectively, particularly to sensitive subpopulations who may not be English speaking, who may be low income people, who are not going to be able to use the same kinds of communication techniques that we do where you are looking in a big, giant booklet with 700 pages of recommended fish consumption advice. So, we have some really neat things in volume four that the states have come up with on how to communicate effectively.

[Slide]

Of course, we use our own equation to come up with our national recreational fish consumption advisory. This is the one that we use. Of course, we use the NAS recommended RfD of 0.1 ug/kg body weight per day. We assume the body weight of 65 kg, looking at that as a woman's body weight. We looked at a meal size as 8 oz

uncooked. Then, the concentrations of mercury that we looked at before we put together our advisory were all the ones that had been submitted to us by the states for our national listing of fish and wildlife advisories. That is what that NLFWA stands for. I am going to show you a chart that gives you all that concentration information in just a second.

Basically, what we do is we take the maximum daily fish consumption rate, equal to the RfD times the body weight, divided by the concentration in the fish, and what I will show you next is a slide that shows the concentration of the fish and what that equates to in terms of a daily fish concentration rate.

[Slide]

When we look at this table, and that is using that calculation, if your fish concentration is 0.1 ug/kg, then you could eat nine meals per month. If it is 0.2, you could eat 4.5 meals per month, and it goes on down. This is generally how states will set up their fish consumption advisory. They generally do not say don't eat any fish at all; the consumption rate is zero. Instead, what they do is, based on the data they have about the concentration of their fish, they recommend a consumption rate because they want people to eat fish; they want to keep the fishery open as much as possible. So, they will always produce their

advisory in the form of what they recommend for fish consumption of specified species that they have concentration data on.

[Slide]

If you look at this, the 4.5 meals per month comes right in at about 0.2 and you will see how we came up with our concentration rate to fit our national recreational advisory for the country. What we have here is a whole huge set of data that the states have given us of mercury concentrations they have monitored in their fish over the years.

I am going to get to the statistics now. We had 66,000 samples from 8,000 stations, and that was provided by 44 states to make up this analysis that we did for the national recreational advisory. Alaska and five other western states did not provide any data at all. So, these 44 states that we have are missing information from Alaska or for those five western states.

However, if you look at the N over here, the sample size number, generally we have at least a hundred or more for each species, and in some cases thousands of samples. We have the mean mercury concentrations if you go along the bottom axis, the X axis. If you come up at the one meal per week number, it would be 0.16 ppm. As you can see, that is protective for most of the species. It looks

like it is over-protective for those species at the bottom of the graph where the line is to the right of those concentration numbers. However, if you look at those species, and we also did this analysis, they are generally ones that also have high PCB constituents.

So here we go again, this is a mercury advisory, however, at the same time we don't want to focus only on mercury and then recommend that people eat lots of fish that may be high in PCBs. So, what we decided to do, and this was a judgment call, is to call it at one meal per week because that would be protective for most species for mercury and it would not be, we felt, too over-protective for the species that were kind of low in mercury because in the 44 states that gave us data on those fish, they were high in PCBs. So, again, a judgment call--we came up with one meal per week.

[Slide]

Here is the test of what we said. First of all, we directed this not just at women of childbearing age but also nursing mothers and also young children. We recommended one meal per week for untested waters. This would be waters in which no one has any idea what the fish concentrations are. From our national database of mean mercury concentrations we wanted to give some kind of rule of thumb to the public when there was no testing

information available; no advice available from their state health department or tribal health department. So, in that case, for that untested water we are recommending one meal per week.

Because of the confusion over FDA also giving advice at the same time, and we did coordinate very closely on the release of our information with FDA's, we wanted to make sure and recognize this. So, what we said is for commercial fish we are recommending that you follow the FDA advice, and then we go on and say for the highlighted area here, in yellow, therefore, if in a given week you eat 12 oz of cooked fish from a store or restaurant--the commercial fish covered by the FDA advice--then do not eat fish caught by your family or friends that week.

So, again, we tried to follow the model of those 11 states that currently give commercial and recreational advice. We recognize that people will eat a mix of fish generally in their diet. So, if you are eating the full amount that FDA recommends for commercial fish, we are recommending that that week you do not eat your own fresh caught fish.

DR. MILLER: Dr. Southerland, five minutes.

DR. SOUTHERLAND: Thank you, I am almost done.

[Slide]

We also went on to say EPA recommends that women who are or could become pregnant, nursing mothers and young children follow the FDA advice for coastal and ocean fish caught by family and friends. Again, our advisory was for lakes and rivers. Generally, the commercial fish cover the marine types of fish. So, we are also recommending that they follow FDA advice if they are catching their own ocean and coastal fish. Then we go on to talk about other sources of protein.

[Slide]

I just wanted to throw this in because we were excited to have the NHANES data also. We did a little different analysis than what was presented yesterday, and I am sure all of us will be doing different analyses over time. But when we took the NHANES data, of course, we wanted to look at the split out if you followed our advice, if you had just one fish meal per week.

So, what we did is look at the total mercury blood levels, along the X axis, for those people who ate more than one per week or those people who ate less than one per week. What we saw for those people who eat one or more meal per week is the blood levels at or above 5.8 ug/L, which corresponds to the NAS EPA RfD of 0.1, and 15.3 percent of them were at or above the 5.8 ug/L. For those

who ate less than one meal per week, it was 1.9 percent at or above 5.8.

So, when we look at this data, and everybody has their own interpretation as we heard yesterday, we feel like we have come up with a good recommendation for people to keep those blood levels at a reasonable level of one meal per week for waters that are untested and you have no idea what the fish contamination is like in those waters.

[Slide]

We have done a lot of outreach on our advisory. Our advisory, remember, includes this connection to the FDA advice. We have worked with ATSDR to distribute this to pediatricians and obstetricians throughout the country. The 12 states that have statewide advisories, and that includes Alaska who says eat as much as you want, we have not sent this information to because we did not want to confuse the public. Those states that have their own statewide advice are free to give their own advice, but to those states that do not cover all their waters and have a lot of untested waters, we have sent this information out.

We have advisory brochures now translated into seven different languages. Those are more generic advisories, not just for mercury, on how to trim and clean the fish to minimize your exposure to contaminants. Then, we have participated in many medical conferences. We even

go to the midwives conferences, as well as pediatricians and obstetricians to make available our information. That is it.

Questions of Clarification

DR. MILLER: Thank you. Questions or comments? Dr. Russell?

DR. RUSSELL: Thank you, that was very clear. There is some confusion about serving size and how 8 oz was picked. Could you clarify that for us? There was some data shown yesterday where the serving size that a woman actually eats is more like 2.6 oz.

DR. SOUTHERLAND: Yes, the 8 oz came from what generally the state health departments had asked us to use as a recommended meal size. Jeff, do you have any more detail? We do all of our advice in conjunction with the states because ours is not a regulatory program; it is only a technical assistance program. The states have generally used 8 oz uncooked, which works out to 6 oz cooked for an adult.

DR. RUSSELL: They may use it, but I am wondering does anybody know the origin of that.

DR. HOTCHKISS: Joe Hotchkiss. I am just curious, to your knowledge, do all states or localities that have advisories say something to the effect that if you are pregnant or could become pregnant--

DR. SOUTHERLAND: Of childbearing age, yes, generally. Jeff, is there any exception to that?

DR. BIGEL: [Not at microphone; inaudible]

DR. SOUTHERLAND: His question was is there any exception to states? Do some states not say women of childbearing age? Do they say only pregnant women or something more restrictive?

DR. BIGEL: [Not at microphone; inaudible]

DR. SOUTHERLAND: But generally when they say women, they say women and children together.

DR. HOTCHKISS: Thank you.

DR. APOSHIAN: I have two questions, one very short one. Does the EPA have data going back, say, 25 years on fish from a given lake and whether the amount of mercury contamination is increasing?

DR. SOUTHERLAND: Actually, the oldest data would be from the '80's. Jeff, is there any analysis that shows that it is increasing or staying the same?

DR. BIGEL: I am not familiar with that analysis. [Not at microphone; inaudible]

PARTICIPANT: I am not aware of data directly in fish, but there are studies that are done [not at microphone; inaudible] and that shows low levels of industrial leaching [inaudible] and then sort of leveling off [inaudible] but there has been about 80 percent

reduction in use of mercury in the economy. So, we expect to see some reduction [inaudible].

DR. SOUTHERLAND: In our data set, which is just late '80's and '90's, we are not seeing a change but that is not really long enough to see much of a change.

DR. APOSHIAN: The other question I have, perhaps you or someone might comment about it, I heard this morning that--and I want to be certain that it is correct and that is why I am asking for comment--that in those fish that have a high amount of mercury, as I understand it, and it is very important that it is clarified, those fish have a lower amount of essential fatty acids; that there is an inverse proportion. Now, we have Dr. Mahaffey here who is an icon as far as this sort of thing is concerned. She was very much involved in NHANES.

DR. SOUTHERLAND: I am going to have to call on Kate for the fatty acid issue.

MS. DEROEVER: Excuse me, could the speakers in the back please come to the microphone and introduce themselves so we have it on the record?

DR. MAHAFFEY: I am Kate Mahaffey, from U.S. EPA. One of the things I have done recently is to sit down and look at some of the data on concentration of mercury in fish and the concentration of a couple of the essential fatty acids in the fish because the essential fatty acids

are frequently cited as one of the major reasons for achieving benefits of fish consumption. There are data that show that certain fatty acid in fish are important for the neurological development of the central nervous system of the fetus. The abbreviation is DHA, and it is docosahexaenoic and it goes on from there.

I looked at the species of fish that are the highest in mercury concentrations, the ones where the advisories are, which include tile fish, shark, king mackerel, swordfish. They are not particularly high in this DHA fatty acid that is essential for neurological development in the fetus. What the essential fatty acids seem most closely tied to is the percent fat in the fish which, of course, makes sense. So, you are not really having a tradeoff between how much of the essential fatty acid you get. In other words, it is not a one to one correlation. You can select fish that are relatively high in essential fatty acids, things such as salmon, things such as some of the mackerels, and are comparatively low in mercury.

On the other hand, if you look at swordfish, tile fish, king mackerel and shark, they are relatively more lean fish and are comparatively low in essential fatty acids. So, it is not as though you give up the nutritional

value. You simply have to exercise wise choices in the kinds of fish you select.

I have not done this for another fatty acid that has an interesting acronym EPA, not us, because the nutritional content of fish is cited as a benefit in terms of coronary heart disease, yet, there are some interesting data out of Europe, specifically out of Finland and also a multicenter trial, longitudinal cohort studies, and for some reason they measured mercury. I honestly have no idea why they measured mercury in people's hair or people's nails, but what they found is that when the person's mercury exposure had been relatively higher, and in the Finnish cohort the demarcation was two or more parts per million in hair, the risk of coronary heart disease and the risk of deposition of fats in the carotid artery, and they imaged the carotids, was higher. So, again, what is going on at least in this Finnish study is that the higher exposures to mercury seem to attenuate some of the benefits of fatty acids and the nutritional benefits of fish.

Again, it is one of these deals where, depending on the fish that is chosen, you get more or less benefit of the diet. People have said the Finnish study stands alone; we shouldn't ignore all the other studies that show benefits. The Finnish study appears not to stand alone because I am now told that there are reports coming out

from a multicenter trial in Europe that are showing a parallel kind of finding.

You can't ignore decades of advice on nutrition, but I think we can expand that advice in a way that gives people the benefits of fish without necessarily the higher exposures to mercury. So, for both the essential fatty acid that is important for CNS development in the fetus and also the risks of coronary heart disease it appears that you do not have to give up the nutritional benefits of fish in a tradeoff for mercury because it is not any sort of one to one correlation. It has as much to do with how fat the fish are in terms of the percent lipid in body composition as anything else.

DR. MILLER: Dr. Lee?

DR. LEE: Basically, I have the same question about mercury over time in fish. So, just to clarify that, one comment about the total mercury--I take it total mercury is not methylmercury that we are talking about over time.

DR. SOUTHERLAND: Oh, no, it is methylmercury that is measured in the fish.

DR. LEE: But in environmental exposure that increased and has now plateau'd.

DR. SOUTHERLAND: I have to refer to Arnie on the sediment core data. Arnie?

DR. KUZMACK: This is Arnold Kuzmack, EPA. That is total deposition of mercury of all sorts, mostly ionic mercury that is deposited. That is the source of the mercury that gets methylated in the aquatic environment and accumulates in the fish. Most of the methylation, of course, occurs in the top layer of the sediment at the bottom.

DR. LEE: And you are saying that is in the lake beds? That kind of work has also been done on Antarctic cores?

DR. KUZMACK: What kind of cores?

DR. LEE: In the ice in Antarctica.

DR. KUZMACK: Yes, there is some work on ice cores as well which I think shows a similar pattern. Lake core is done in various locations and typically shows peak levels, say, two to five times the preindustrial levels and what that is sort of depends on where you are located. If you are near industrial areas it is likely to be a higher ratio.

DR. LEE: Thank you.

DR. MILLER: Dr. Fischer?

DR. FISCHER: I would like to ask whether the EPA recommends to the states the use of the EPA RfD for everyone--women, children and other adults, or do they

recommend a different set of restrictions for those two groups, adults versus women and children?

DR. SOUTHERLAND: Right now we just have the 0.1 on the books for developmental effects. Because it is listed for developmental effects we are recommending it for women and children, but we have not taken a position on this two-tiered approach that some of the states have done. We do not have an IRIS value right now. It varies for the general population.

DR. FISCHER: Why is that, that you don't do that?

DR. SOUTHERLAND: Kate, I would have to ask you, the IRIS program is our official?

DR. MAHAFFEY: Right. The way EPA's reference does this work is that they are set for the most sensitive subpopulation. It is not the most sensitive member of the subpopulation but the most sensitive subpopulation. Since most of what we deal with does not know boundaries in the sense that if you deal with an air contaminant or water contaminant you can't very well separate out the exposures for men, for women or for children, the underlying philosophy has been that you work to protect the most sensitive subpopulation. While this approach of a two-tiered advisory may be effective when you are dealing with a limited distribution or self- or family-caught fish, it

is harder to enforce who eats the fish if it is winding up in commercial sales.

DR. FISCHER: You know, it seems to me very hard for you to convince people that fish is good for them and that there is benefit of eating fish if you are regulating in that way. In other words, why are you restricting the consumption of fish to men of my age when, in fact, we aren't the most susceptible?

DR. MAHAFFEY: Well, until we know more about the cardiovascular risk, I don't know that I am ready to go there.

DR. FISCHER: I mean, I can't believe that you don't believe the immense literature out there on the benefits of fish consumption.

DR. MAHAFFEY: If you look closely at the studies, they are not unequivocally supportive of the benefits. Some of those studies are mixed, and it is quite possible to choose kinds of fish that result in low mercury. As you can see with the NHANES data that we showed, while the percent of people who eat fish one or more times a week is a lot higher, in the 6 and above blood level, 85 percent of those people were able to select fish that are comparatively low in mercury and have blood values under the reference dose. So, it is more to do with the

kind of fish selected than simply fish consumption. It is as much which fish rather than fish or not.

DR. FISCHER: I understand that, but you can see the number of states who disagree with you here. Look at the number of states who have the two-tiered approach and are using it.

DR. SOUTHERLAND: There are 16 states that have the two-tiered approach. It is a little confusing from the way I had to present the graph but 16 states do both. The other states, and there is a total of 43 that give advice on mercury, will use a consistent RfD. So, this is a new thing that states are starting to work on, the two-tiered approach.

I am going to have to make a point of clarification here, though I don't want to interrupt the conversation between you and Kate, but we have no regulatory authority. EPA has no regulatory authority. All we do is talk to the states about advice, and the states have no regulatory authority. When they give advice on recommended meals, they are not seizing those fish out of people's hands and taking them to jail, or anything. They are just giving advice; we are just giving advice. There is no regulatory authority in EPA. FDA is the only agency that has that.

DR. MILLER: Dr. Russell?

DR. RUSSELL: There is a lot of interest now in DHA and EPA with regard to membrane stabilizing effects and sudden death, prevention of sudden death. Is there any data that high levels of mercury cancel out that effect? Because this is totally different from coronary-artery disease.

DR. MAHAFFEY: I am assuming you are addressing that to me. As I recall the Finnish study, there was a greater incidence of mortality in the people that had the higher mercury levels. As you say, it gets into the underlying mechanism of oxidation and heavy metals such as mercury to promote oxidation.

DR. RUSSELL: Well, these fatty acids specifically stabilize membranes. It is a physical-chemical thing.

DR. MAHAFFEY: Right, but it is a highly unsaturated fatty acid.

DR. RUSSELL: Yes, but it may not just be from oxidation.

DR. MAHAFFEY: Exactly. Again, I am recalling this data from memory. I would be pleased to follow-up and provide the paper to you.

DR. RUSSELL: Thank you.

DR. MILLER: Dr. Aposhian?

DR. APOSHIAN: I think it might also be a good idea, since we have Kate here because I have learned some things this morning that are very educational to me anyway, as you know there have been questions about the 60,000 children at risk that the National Academy of Sciences report pointed out. Yesterday some people questioned this as being too high. I believe Kate has some data that she might want to share with us, suggesting that the 60,000 National Academy of Science figure is too low.

DR. MAHAFFEY: Again, this is from memory. I would be glad to go back and get the specific numbers, but as I am recalling this, there are about four million births in the U.S. per year. If you take the NHANES value, the 99 alone showed about 10 percent of women with blood mercury of 5.8 and greater, the combined 99 2000, the number turned out to be, I think, about 7.8. So, somewhere circa 8 percent. If you take 8 percent of one million, you are coming out with about, I would think, 320,000. If you take the 10 percent, it is 400,000 newborns a year. If you apply the NHANES data and the number of births, that would be the estimate of the number of infants born each year where you would expect to see their initial blood mercury higher than the value that EPA believes to be safe. So, we don't think the 60,000 is too high. If anything, the data suggest it is comparatively low. I am sorry, 10 percent of

4 million would be 400,000; 8 percent would be about 320,000.

DR. DICKINSON: [Not at microphone; inaudible]

MS. DEROEVER: Dr. Dickinson, would you please use the microphone?

DR. MAHAFFEY: I see what you are doing, 60 million women of childbearing age approximately, the data show about 9 percent in that age group in a given year are pregnant. There is another number, I think it is 6.5 pregnancies per 1000 women. You know, we went through the math.

DR. FISCHER: I would like to ask you to give us the calculation that you are speaking of--

DR. MAHAFFEY: Sure, that is fine.

DR. FISCHER: --so that we have it to look at.

DR. MAHAFFEY: No problem.

DR. MILLER: Dr. Scherer?

DR. SCHERER: Yes, Cliff Scherer. I wanted to ask a question about the extent to which we have any information about the effectiveness of advisories. Do you know about to what extent states or how people are following advisories?

DR. SOUTHERLAND: There have been some individual studies of that. Actually, we have been working with Cornell University and some others to do effectiveness

measures. That risk commercial guidance document that we have actually has the best literature review of that type of effectiveness data. What they have generally concluded is if you are talking about educated, middle class people who are doing it for recreational purposes, those books that the states will give you when you buy your fishing license are fine. But when you are talking about people that have English as a second language or who are not buying fishing licenses, then that is obviously totally ineffectual. What they have found is that things like posters--certain types of cultures react very well actually to comic book style posters. They also have posting in different languages that can be effective, and also big press events. Each year when a state updates their advisory, if they do a lot of press work. ORSANCO has been doing a lot of the effectiveness studies because they do the fish advisory publicity for all of the Ohio river basin. So, anyway, we have some good information on what works with what populations.

DR. SCHERER: Do we know anything about the percentage of people that are paying attention to those kinds of messages?

DR. SOUTHERLAND: I don't know if we have any percentage information. I know in the Great Lakes, for example, they have done a number of studies and in the

Great Lakes, because it is such a high group that are eating fish, it is very well publicized. Also, in the Ohio River Basin I think they are getting fairly high effectiveness levels. In other parts of the country, not at all because, again, it is the level of publicity and the type of publicity.

That is why when we have sent our posters out, we send them to the pediatrician and obstetrician offices for them to post right there. The women and children health clinics also like to get that kind of poster effect as opposed to a 700-page textbook.

DR. MAHAFFEY: Michael Bolger told me that the calculation, I guess, shows around 350,000 to 400,000 is in your books.

DR. BOLGER: If you look at your figure, you will see it gives you the number of women where it says 7 percent, but it is actually more like 8 percent based on data from Susan Schober. So, the number of women on annual basis who are pregnant is about 276,000 women. That is on an annual basis, the number of women who are pregnant who exceed the reference dose is about 276,000.

DR. DICKINSON: This is Annette Dickinson. We had some discussion yesterday about the fact that that includes the ten-fold safety factor.

DR. BOLGER: That is correct.

DR. DICKINSON: So, given the fact that they exceed the RfD with a ten-fold safety factor and the effects on which the whole bench mark dose is based are effects in the most sensitive population, what is the implication of that, that they exceed the RfD? Does it just mean their safety factor is less, or does it mean they are actually at risk?

DR. BOLGER: This is what I am going to talk about tomorrow. What implications you draw really are some of the things I am going to try to address tomorrow so I would hate to get ahead of myself today. But it is a very good question.

DR. DICKINSON: But we are thinking about it today.

DR. BOLGER: I understand. The margin of safety issue is what you are getting at.

DR. MILLER: Ms. Halloran?

MS. HALLORAN: To go back to the point raised just a minute ago about consumer awareness, the Northeast States for Coordinated Areas Management, which is an association of air pollution agencies in the east, reported in May, 1999 in a survey that they apparently did that of about 75 percent of their respondents who eat fish on a regular basis, about half said they knew about advisories

issued by states or FDA and one-third said they knew what they meant.

DR. MILLER: It is actually the question that I had, what data was there that looked at understandability? I mean, reading that advisory, the combined FDA-EPA advisory I found it totally confusing. Now, I may not be as clever about this as people who live near lakes, but I found that totally confusing. There are three messages, all in one document. I was just curious as to what kind of research was done.

DR. SOUTHERLAND: We have not done any consumer research on our advisory because it is so new, but we do know that the 11 states that are currently giving both commercial and recreational fish advice have dealt with this issue before of how to do the tradeoffs between what you get from a store or restaurant and what you get caught by yourself.

So, we just followed their model in putting out our advice because, otherwise, it looked like the two were totally unrelated. We were saying one meal per week; FDA was saying 12 oz. They are entirely different species involved.

DR. MILLER: Mr. Scholz?

MR. SCHOLZ: Brandon Scholz. I wanted to follow-up on a point that you made on EPA's outreach. You said it

appears that most of your outreach is to healthcare professionals who deal with pregnant women.

DR. SOUTHERLAND: And fishery groups, like the American Fishery Society.

MR. SCHOLZ: Do you do any other outreach to retail or to restaurants? Any other distribution of your materials?

DR. SOUTHERLAND: No, ours is strictly directed at recreational fishing groups, like Bass Masters and American Fishery Society, as well as health groups. The lead-off statement for us is fish caught by your family and friends. So, we do not cross over into the commercial fish advice at all. If anyone ever asks about commercial fishery we cite the FDA advice. Again, EPA has no regulatory authority for fish consumption advisories. We are strictly for technical assistance to the state health departments.

DR. MILLER: Some of you may have wondered why I have allowed this to continue on, not exactly my usual style for these kinds of things. Not only is it an important issue, but our next speaker is not here.

[Laughter]

I just don't want you to get the wrong idea. Johanna?

DR. DWYER: I wanted to agree with Dr. Miller that I found the advice a little confusing, and I kept coming back to the thought that for fish there are no recreational uses if you are fishing and you are the fish.

[Laughter]

I am also taken by some of the problems we hear on the dietary guidelines committee on the alcohol recommendations. You know, if you think about it, most of the problems with alcohol seem to come from the ethanol. Simplifying the advice to something where you can focus on that with a very, very simple message I think has gotten through to a lot of people, whereas 25 or 30 years ago it didn't.

I guess what I am struggling with, and perhaps Dr. Miller is as well, for those of us who have to give a five-second sound byte in a clinic to a patient, I really need something that is a sentence or maybe two sentences.

DR. SOUTHERLAND: I think the way we have tried to hone in on it, and I hate to say it because, again, the focus groups have struggled with this, but it is the species type. We deal with freshwater fish, fish that you would catch from a river or a lake. The marine species are generally the predominant commercial species. Now, what is the public's understanding when they see a species name as

to whether it is freshwater or saltwater? That is where the confusion is coming in I believe.

EPA's original recommendation for FDA was to try to do lists of species and, apparently, the focus groups just found that too confusing. Because if we had done a list of species, then we could have had unified advice from both EPA and FDA. I believe we could have worked that out but it was just too much detail.

MS. HALLORAN: I hope I understand this correctly, the whole origin of the problem of EPA and FDA having to give different advice doesn't really come from a separate evaluation of the safety of freshwater fish and ocean fish. Ocean fish is not safer than freshwater fish, if I am correct. It is that FDA has made basically different judgments in the risk analysis. Is that correct?

DR. SOUTHERLAND: And it is also the concentration of the species. I gave you the data that we have, and we have, again, 66,000 samples from 44 states and we are looking at our concentrations. I believe FDA is a little bit inhibited as they don't have as up to date data, and I don't know that they have as much data on their marine and coastal species as we do for our lake and river species. So, they were also looking at the concentrations that they had in their database.

DR. MILLER: It seems to me, in response to that, listening to this discussion, it is not only that issue. That is one issue. The other issue is the fact that this increases the number of species that people have to worry about, and that is the problem with people saying they get confused when they see these lists even if they are identical. Indeed, if FDA lowers its action level, if you will, its advisory level, that species list would increase even more. The question from a procedural point of view is how do you give this advice to people in a way that they will use it and can use it? As far as I can hear, that problem has not been resolved.

DR. HOTCHKISS: I want to make sure of your last statement. FDA is using an ADI of 0.4; you are using an RfD of 0.1. That is a four-fold difference. If you run through the calculations, that seems to me to be a major difference in the two agencies' recommendations. Granted, you have different databases and so forth, but the major difference is simply that either acceptable daily intake or reference dose, or virtually safe dose or whatever you want to call it, is a four-fold difference between the agencies. Is that correct?

DR. SOUTHERLAND: Yes, that is correct, but they also did look at their concentration ranges for saltwater fish compared to the concentration ranges for what we have

in freshwater. At least in the lower 48 states our freshwater fish can be much more contaminated in some cases, particularly certain water bodies that have higher levels of mercury sometimes. Again, we were working with a richer database and also concentration information. But, yes, you are right, it is a combination of concentration and RfD difference.

DR. MILLER: Johanna?

DR. DWYER: I was very much surprised and pleased by the enormous number of chemical analyses that you have done on the mercury concentration of selected fish. I think it was in our handout. Does that go in any databases that are available on computer programs?

DR. SOUTHERLAND: Yes, those are all the data that have been submitted to us by the states that do this monitoring and it is all on our web site. We have it all.

DR. DWYER: No, I meant databases like the kinds of things people put on a laptop computer and dieticians use for example.

DR. SOUTHERLAND: We haven't provided to those groups but they are readily available on our web site. Again, it is all voluntary. The states don't have to give us this information at all, but since 1993 most of the states have been giving us tons of information, not only

information on their advisory but on the fish concentrations that they have monitored.

DR. DWYER: Is it collected in a random--how is it done? How do you collect the data on these fish, and does it go into the standard reference database of the food composition for U.S.A.?

DR. SOUTHERLAND: To my knowledge, it only comes to us on a voluntary basis. Each state has their own monitoring plan. Some have a rotating basin approach and for each year they try to go to another basin and they measure fish tissue. Others have a regular, you know, station that they monitor each year. It varies by the state and we take all the data they give us because it has all been through state QA/QC and their laboratories, and they are using it to make their fish consumption advisory decisions so it is good enough for us.

DR. MILLER: Mr. Scholz?

MR. SCHOLZ: I would like to ask one more question. You had mentioned that there is a Cornell study in place, or it has been done, gauging the effectiveness of the advisories?

DR. SOUTHERLAND: Cornell has an investigator up there that we have worked with that has done these effectiveness studies. She has worked in the Great Lakes area and she has also worked in the Ohio River Basin.

DR. MAHAFFEY: There is also additional work in the State of Maine on interpretation of the advisories and risk commercial evaluation process understanding. So, it is not as though this is a totally untapped area.

MR. SCHOLZ: No, I understand that. I was just curious, is that a study that we can get? I mean, is that available to us? My question was is it ongoing or is it done?

DR. SOUTHERLAND: She has some that are ongoing; she has some that are under way. So, I can get those to you, sure.

MR. SCHOLZ: It would be interesting because generally coming from the Great Lakes and the Wisconsin area, you know, there is the annual story in the newspaper at the beginning of the year that says, in short, all fish have mercury; don't eat it. So, I would be curious what the study says because it doesn't seem that the way the press reports it is fair because it doesn't necessarily differentiate which fish, what level, for whom and, unfortunately, it is not a good way to come up with what we are trying to do.

DR. SOUTHERLAND: I know that certainly in the Ohio River Basin where she did her study there is a big drop-off at the time of the press release. She did the analysis and she actually did a time series thing right

around the press release she did questionnaires, telephone surveys and, of course, fish advisories. Then she did it several months later and then several months after that and, of course, it really drops off over time. That is why I think people are looking for things that are more permanent, like posters, signs or something either in the health clinics or actually at the point of fishing as something more substantive than just a big press release. Again, you know, our risk commercial document, and I can get you that also, has tons of references of the studies that have been done to look at effectiveness.

DR. MILLER: Dr. Busta?

DR. BUSTA: I would like to get back to this collection of data from the states. Do you have a distribution as to which states do the most analyses, and are they the states with the greatest pollution? Maybe the states with greater pollution, are they sampling more and are they sampling mainly the polluted areas? Have you any kind of information like that?

DR. SOUTHERLAND: Well, actually it started like that in 1993 when we began our program and I could say definitely yes, everything that was in the database was from suspected problem areas. What has happened though, over time as people have become more and more concerned about mercury, and that is why they are starting to see

these 12 statewide mercury advisories, as they went to more and more sites and checked to see if they had mercury concerns, they then said, you know, let's try pristine areas.

This is what they did in Maine, for example, and that is when they found that even their pristine areas that did not have a discharge or a point source discharger, they found levels of concern for the mercury. That is why you see more and more states having these statewide mercury advisories because they just said what are we doing here? I mean, there is no sense waiting when we even have pristine areas because of the atmospheric deposition contributions of mercury. We are just going to go ahead and have some general recommendations statewide, and then we will continue to try to go water body by water body and confirm or deny that assumption. But right now that is what the statewides are based on, a general understanding that no matter where they looked they had some species that had concentrations of concern. It is an ubiquitous problem, it truly is.

DR. FISCHER: I would like to see if we could get some information on the overlap between regulated commercial fish and sport fish--

DR. SOUTHERLAND: I am sorry, I lost you.

DR. FISCHER: What I am trying to see is what is the overlap between sport caught fish, which EPA regulates, and--

DR. SOUTHERLAND: We don't regulate; we give advice through the states.

DR. FISCHER: Excuse me, I made a big mistake there. I am sorry, I should have learned that by now. And, fish that the FDA takes care of, commercial versus sport caught. In the Great Lakes basin you can buy whitefish and walleyed and a lot of what we would call sport caught fish, lake trout. So, here are sport fish that are commercial fish. I just wonder how much of the total consumption is confused in this way.

DR. SOUTHERLAND: There is definitely an overlap and the 11 states that have that little box in there that says they are giving commercial advice as well as recreational, they are the ones that definitely came up with this, and you will see there is a lot in the Great Lakes area because they said what difference does it make if they go down and catch this fish themselves or if they go to the nearby fish market where the fish that somebody else caught was put and they purchased it? There didn't seem to be any reason for there to be a separation. That is why the state health departments have decided to give advice across the board. Like I said, 9 of the 11 states

that do this include tuna in their recommendations because they have found so many people were eating tuna fish sandwiches and then adding onto that their recreational or other commercial fish. So, they felt that they had to include the tuna fish in their advice too.

DR. FISCHER: Michigan hasn't dealt with this problem at all, and they give no advice on purchased sport caught fish. I can't remember seeing other Great Lake states give it either. I know that creates confusion in the public's mind as to what they should do.

DR. SOUTHERLAND: Several Great Lake states-- Henry Anderson was going to speak next and I know he gives that type of advice. Pam Schubat, in Minnesota, does. We have a number of states that give combined advice for the Great Lakes states.

DR. MAHAFFEY: Just one comment, mercury, while it is a local problem in that there can be local discharge and local deposition, is also a national problem. Part of the mercury that goes into the environment enters a high atmospheric level pool of mercury that then can be deposited in precipitation. For example, it is the United Nations environmental program that this fall will do an assessment of mercury. The European Union has adopted U.S. EPA's reference dose for mercury and, again, is doing broad work on fish in Europe because of concern for mercury.

There is not a clear separation between "locally caught fish" and fish that wind up in the commercial market. They come out of the same water.

DR. MILLER: I think I am going to bring this discussion to a close. I think the point has been made. I think what is abundantly clear to me is that we are not really very close to a really effective communication system to get a relatively simple message that enables people to make appropriate decisions themselves. I doubt that we will come up with anything better in our time but we ought to be thinking about how to approach this particular problem.

I also think that we have spent quite some time this morning emphasizing the importance of the issue. I am certain that this committee has a general recognition of the significance of the program and the importance of doing something about the problem. I think the debate that we are having over which number to use is important in implementation of any plan, but I don't think it reflects the fact that the members of the committee in any way take this thing as anything but quite seriously.

So, at this point I am going to call this section closed. Thank you for this discussion, and we will move on to our next speaker. I assume Dr. Henry Anderson is not here. So, the next speaker is Dr. John Middaugh, from the

Alaska Department of Health, talking about the Alaska advisory.

Alaska Advisory

DR. MIDDAUGH: Chairman Miller, and members of the Food Advisory Committee, I am John Middaugh, State Epidemiologist with the Alaska Division of Public Health. I am here today to provide information to the committee on behalf of the State of Alaska as a public health physician with responsibility for protecting the health of the citizens of Alaska. Thank you for providing the opportunity to bring to your attention Alaska's experience with fish advisories for methylmercury.

I am pleased that the Food and Drug Administration is having this meeting. I believe that the committee has an important opportunity to clarify roles in attaining shared national goals to protect the environment and to protect the public health. To do so, it is essential to sort out federal agency authority and responsibility and to respect the balance between federal and state authority and responsibility.

We also have before us new technology that can help us further scientific understanding. Finally, we can ensure that we behave ethically, adhering to fundamental principles of "do no harm" and weighing benefits and risks.

Alaska's experience with national fish advisories has uncovered several major areas of concern and revealed potential unintended adverse consequences. Current national recommendations, a "one size-fits-all" approach, do not make sense in Alaska. National recommendations for fish consumption are not consistent with available evidence and are not consistent with Alaska recommendations.

Considerable scientific controversy exists over the risks of low-dose methylmercury exposure. Data linking low-level methylmercury exposure to adverse health outcomes are weak. Adverse neurodevelopmental outcomes documented are subclinical, detectable only by sophisticated tests of unknown long-term significance. Results may be limited by potential confounding. Leading studies have not found similar results, and ongoing studies hold the promise of providing important information in the near future.

Advisories based upon risk assessment without consideration of well-established public health benefits of fish consumption have great potential to harm public health if reductions in fish consumption occur. We have special concerns over the impact of fish advisories for Alaska natives and rural resident subsistence consumers who have few alternatives to fish. The public health harm caused by fish advisories has been well documented, especially in Canada. Fortunately, data from Alaska provide evidence

that most, if not all, Alaskan exposures to methylmercury are below those of current concern, even applying conservative models.

Finally, extensive international scientific investigation of Arctic contaminants under the Arctic Monitoring and Assessment Program of the International Arctic Science Council during the past eight years has led to the consensus Arctic recommendations that the health benefits of Arctic subsistence foods outweigh potential risks, and that local public health authorities need to take into account local information to craft dietary guidelines.

We have a substantial body of scientific information on mercury in Alaska. I would like to provide a brief summary of some of the most germane studies that provide evidence that determined Alaska's current dietary recommendations.

I have provided a detailed copy of handouts because there is a lot of data and I know that I can't present it in 20 minutes.

[Slide]

First, we analyzed ancient human hair from mummies from the Aleutian Islands in Alaska. The mummies were taken from islands out in the Aleutian chain during

the 1920's when archeologists collected human remains and artifacts from burial sites.

[Slide]

This is an adult wrapped in reed tissue, and then underneath that wrapped in seal skins.

[Slide]

This was an infant in a basket.

Our goal was to try to establish if methylmercury was present long prior to the industrial revolution and, therefore, represented naturally occurring exposure. After receiving permission from the Aleut Corporation and the Museum of Aleutians, we collected hair samples from four infants and four adults that radiocarbon dating established to be approximately 550 years old, dating to about 1450 A.D.

[Slide]

The average level of methylmercury mercury in adults was 1.2 ppm in hair, and in infants was 1.44 ppm, with a range of 7 ppb to 4.61 ppm.

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Segmental hair analysis showed patterns of higher and low methylmercury in centimeter segments, compatible with seasonal and event-specific changes in mercury exposure through a subsistence fish and marine mammal diet. These results are consistent with a few other similar

studies of mercury in ancient human remains, supporting the hypothesis that humans have always been exposed to naturally occurring mercury through fish and marine mammals in the diet.

Unlike many areas in the continental United States, there are no local industrial sources of mercury in Alaska. Extensive environmental sampling during the past ten years has documented that Alaska is one of the most pristine areas in the Arctic.

I want to go over the next set of slides very quickly. They show some of the wealth of sampling data of fish species. These results are for 1993 from U.S. FDA. In red, you can see for salmon many of the results are undetectable.

[Slide]

This is from the ATSDR criteria document. Again, salmon is 0.035 ppm.

[Slide]

Again, our Department of Environmental Conservation lab, shows 1999 results and again in red are highlighted the salmon results. They are almost all about 0.025 or non-detectable.

[Slide]

Researchers at our University of Alaska, measuring king salmon methylmercury levels are in this column, here, and all the results are very low.

[Slide]

Those are the same results in a graphic form. All of these are in your packet so you can study them later and figure out which of the species you want to eat, but these are the same results from the University of Alaska.

[Slide]

Arctic grayling, a form of trout, are all levels that are very, very low.

[Slide]

Northern pike are one of the freshwater species with the highest levels in Alaska, but most are also below one part per million.

[Slide]

Alaska freshwater fish, we have turbot, sheep fish, dolly varden trout, sucker fish, rainbow trout, whitefish.

[Slide]

Our Department of Environmental Conservation for southeast Alaska shows all the species are very low except for salmon shark.

[Slide]

Out in the Aleutians there is a small number of samples but, again, Dover sole, ocean perch and yellow fin sole all have very low levels.

[Slide]

Cook Inlet, which is near Anchorage--all very low levels. I would like to skip through this and then I will go on, but in the packet you can see that there is an extensive amount of sampling and of most importance is that the levels of methylmercury in all species of salmon are among the lowest of all species of fish, ranging from non-detectable to about 0.05 to 0.08.

Dietary surveys in Alaska document a wide-ranging exposure to multiple fish species in marine mammals. This overhead presents regional compositions of subsistence harvest by our rural residents in different parts of the State. There are considerable variations by region most notable in amounts of fish and marine mammals. Up in the north slope there is a lot of marine mammal that is whale, seal and walrus. In some of the other areas of the State there is mostly fish and of the fish, mostly salmon.

[Slide]

As you can see, fish comprises about 60 percent of Alaskan's rural subsistence harvest.

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Mean salmon consumption in Alaska far exceeds the current EPA and FDA consumption advisory amounts, and you can see in these dotted lines are the FDA and EPA recommended consumption advisory levels, and these are mean harvest data for fish for different communities in Alaska.

[Slide]

The economic and nutritional values of subsistence foods in Alaska are huge. For the percent of population's required protein overall in Alaska subsistence harvest comprises about 65 percent or protein, 9 percent of total calories. The estimated economic value in Alaska of subsistence harvest is 267 million dollars.

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Currently, several major dietary surveys are under way in Alaska, including ones conducted by the Alaskan Native Tribal Health Consortium with EPA support, the Aleutian/Pribilof Island Association supported by the NIEHSS, the Alaska Native Health Board, supported by ATSDR, and the University of Alaska, supported NIH.

In addition to these traditional sources of information, we also have new data on actual human exposure levels. Dr. James Berner, Alaska Native Tribal Health Consortium, is the principle investigator of an Alaska native maternal-infant cord blood contaminants study. This grassroots project was requested by local Alaska native

communities. Funding of this effort is from EPA and the National Center for Environmental Health of CDC. In addition to actual measurement of heavy metals, persistent organic pollutants and radionuclides, long-term neurodevelopmental follow-up of the children is planned.

Dr. Berner has given permission for me to share with you the initial results from this study. For 52 mothers who delivered babies from the Bethel area of Alaska, the median blood mercury level was 4.65 ppb with a maximum level of 21 ppb, and for 29 mothers from the Barrow area the median blood mercury level was 1.1 ppb with a maximum level of 4.5 ppb. Additional data include hair mercury results for 14 mothers with a median level of 0.94 ppm in Bethel and 0.48 ppm in Barrow, and a maximum level of 1.9 ppm.

Recognizing that these two populations have high subsistence intakes, levels show no cause for concern. The State recently established a statewide maternal hair biomonitoring program to provide, at no cost, measurement of mercury in the hair of all women who are pregnant. We just had the first results that were called in last night of the first 12 women participating. The hair mercury levels ranged from 0.03 ppm to 1.2 ppm, with a median of 0.26 ppm.

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Balancing benefits and risks is essential in crafting public health recommendations. Some of the benefits of subsistence lifestyle are nutrition, taste, sociocultural values, fitness, cost, children's education and ecological knowledge. Some of the risks are accidents associated with hunting and fishing, and health risks include botulism, trichinosis and paralytic shellfish poisoning, for example. Then, there are the risks of not eating the traditional foods, obesity, diabetes and heart disease.

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There are also many sociocultural benefits of traditional foods, what food is to a culture. The Alaskan native people have indicated that the issue of contaminants is the most important one facing them as a community. They have identified values of the subsistence reliance on traditional food and fish as physical fitness, recreation, the healthy foods, being in tune with nature, sharing, that it saves money and the value to their culture. Also, pride and confidence. For their children, their education, the natural environment, survival skills, food preparation techniques, practicing patience and respect.

[Slide]

There are well-known public health benefits from fish consumption. Fish provide high nutritional value,

vitamins A, E and C, protein, energy, omega-3 fatty acids, monolipids, iron and zinc. Omega-3 fatty acids have proven benefits in preventing complications from diabetes, preventing coronary heart disease and atherosclerosis and preventing complications from arthritis, to name just a few. There are also major economic, cultural, spiritual and social benefits from subsistence practices.

Experience in Alaska has documented adverse effects on public health and communities from fish advisories with subsequent abandonment of traditional diets. Alaska natives are experiencing a major increase in the prevalence of diabetes. Heart disease rates are increasing, and recent studies have documented vitamin A and D deficiencies.

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For example, the prevalence of diabetes among Alaska natives has increased substantially in the past two decades. We are concerned that Alaska natives may be on the threshold of a major epidemic, similar to those of the Pimas. In addition, Arctic residents are faced with serious problems of alcohol use, lack of physical exercise and subsequent increases in obesity.

The subsistence lifestyle and diet are of great importance to the self-definition, self-determination, cultural and socioeconomic and overall health and well

being of indigenous peoples. Alaska natives have voiced their fears and concerns about the safety of traditional foods. However, native elders have also expressed concerns that the fear associated with the contaminants may cause greater harm than the actual presence of the contaminants themselves, and that health warnings regarding food consumption should only be made when there is strong evidence that the risks outweigh the benefits.

There is a compelling need to incorporate benefits and risks in dietary recommendations. The precautionary rule seems most appropriate for taking actions to reduce industrial and other man-made pollutants. Alaskans have great concerns over the long-range atmospheric transportation of pollutants into the Arctic. The State of Alaska supports the POPs treaty and efforts to reduce anthropogenic pollutants, and use of the EPA RfD in reducing mercury emissions.

But in creating public health recommendations for fish consumption, it is essential to weigh benefits and risks. Relying on the EPA RfD led to the question what is the public health risk of the uncertainty factor? The Belmont Report provides the foundation for U.S. policies for the protection of human subjects.

The report outlines basic ethical principles, the principles of respect for persons, beneficence and justice.

The Belmont Report formulated to general rules to complementary expressions of beneficent actions. One, do not harm and, two, maximize possible benefits and minimize possible harms. Justice has the sense of fairness in distribution or what is deserved. An injustice occurs when some benefit to which a person is entitled is denied without good reason, or when some burden is imposed unduly. The application of the general principles leads to considerations of risk/benefit assessment.

In this context, the State supports the FDA's leadership in providing general public health-based dietary guidelines, including the flexibility to weigh benefits and risks and providing for substantial involvement of state and local public health agencies in applying local evidence in developing dietary guidelines.

In response to the national fish advisories of January 2001, the Alaska Division of Public Health engaged in extensive consultations with Alaska stakeholders. After reviewing all of the available evidence, the Division of Public Health issued consensus recommendations for fish consumption in Alaska. The most important difference from national advisories is the following:

The Alaska Division of Public Health continues to strongly recommend that all Alaskans, including pregnant women, women who are breast-feeding, women of childbearing

age, and young children continue unrestricted consumption of fish from Alaskan waters.

The State does not support national advisory recommendations to restrict fish consumption to 12 oz per week, nor the national advisory recommendations for pregnant women to restrict fish consumption to one meal per month.

[Slide]

The State, in consultation with the Food and Drug Administration, developed the following language that was included in the amended FDA advisory: Some kinds of fish that are known to have much lower than average levels of methylmercury can be safely eaten more frequently and in larger amounts. Contact your federal, state or local health or food safety authority for specific consumption recommendations about fish caught or sold in your local area.

[Slide]

The following agencies and organizations endorsed and contributed to the development of these recommendations: The Alaska Department of Environmental Conservation, the Alaska Department of Health and Social Services, the Alaska Native Health Board, the Alaska Native Science Commission, the Alaska Native Tribal Health Consortium, the Aleutian/Pribilof Islands Association, the

Institute for Circumpolar Health Studies of the University of Alaska Anchorage, the North Slope Borough, the University of Alaska Fairbanks and the Yukon Kuskokwim Health Corporation.

[Slide]

As part of the State's development of its dietary recommendations, the State also made a commitment to supporting increased monitoring of mercury levels in fish, supporting the ongoing research being conducted by Dr. Jim Berner in his maternal-infant contaminants study, and developing and implementing a statewide maternal hair mercury biomonitoring program. These efforts are all underway.

In conclusion, the State supports increased human exposure assessments such as the recent mercury studies of the NHANES by the National Center for Environmental Health of CDC; increasing human exposure assessments as proposed by the National Center for Environmental Health through expanding the national NHANES assessments to the state level; increased biomonitoring of fish species; increased consideration of benefits as well as risks; targeting fish advisories based on levels of mercury in key species and actual human exposure data; and increased and sustained efforts to reduce global anthropogenic emissions of mercury. Thank you.

Questions of Clarification

DR. MILLER: Thank you. Questions or comments? Dr. Hotchkiss?

DR. HOTCHKISS: I think we would all agree that Alaskan fish are lower in methylmercury than fish available from most other parts of the country, which tells me if you don't throw mercury around in your environment you have fish with less mercury. But my question to you is if the fish consumed in Alaska had methylmercury levels that were more consistent with the rest of the U.S., or at least the higher portions of the U.S., would your position be the same on this issue?

DR. MIDDAUGH: Well, I think that the methylmercury exposure is determined by fish, and I certainly think that there is an absolute need to have fish advisories especially for local contaminated areas. I believe that there is a great opportunity with new technology to make accurate measurement of human levels of mercury, at very little cost, to combine the risk assessment methodologies with actual exposure levels which are showing us, at least in Alaska, that the levels that we actually measure are far below those that we would have predicted to have found having only used data from fish species and these dietary projections of assumed amount of exposure.

I also believe that the data are probably quite skewed, and our experience is that when we monitor fish we find very few that have higher levels and almost all the other fish have very low levels. I think that may be one explanation why we are seeing a disconnect between some of the predictions of exposure levels and some of the exposure levels when we actually go out and measure.

The CDC and the Pugh Commission and the Trust for American's Health have all recommended increased biomonitoring to actually measure what the exposures are that are occurring among the U.S. population for these contaminants, and I think it is critical that we expand that knowledge database before we potentially warn people to avoid consuming a particular fish product that has huge documented public health benefits.

DR. HOTCHKISS: I agree, but I am a little confused by your answer. Do we agree that in general fish caught in either marine or freshwater environments in Alaska are lower in methylmercury content than, let's say, fish caught in the region of the Gulf part of the U.S.?

DR. MIDDAUGH: I can for sure say that the fish in Alaska have very low methylmercury levels. I believe that they are lower than in many other parts of the United States but I am not an expert on the levels in a lot of the rest of the country.

DR. HOTCHKISS: Let's assume for the sake of discussion that they are. I think the data would bear out quite strongly that there is a difference from the Great Lakes, for example. I am just curious about your position. Is your position based on these low levels in Alaska, or is your position in general that we don't know enough about methylmercury nor the levels across the U.S. to make recommendations?

DR. MIDDAUGH: Well, there are certainly two parts to my answer. The first one is that we were very pleased in Alaska, when we found all this data and did our measurements, to find that we have very low levels. That made it much easier for us to develop our Alaska recommendations. But they fly in the face of the national recommendations so we are confronted by having "Brain Food" on the computer that rural Alaska residents download which tell them not to eat their fish, and then what do they eat? We are part of the United States. So, that is a problem.

Then, we also are concerned about the absence of benefit/risk evaluation in the national program. So, I think that the easy part for Alaska is that our levels are lower so it made it easier for us to come to consensus recommendations for people in our State. But we are also very hesitant about the reliance on the EPA RfD for crafting dietary recommendations for the American people.

DR. HOTCHKISS: Thank you.

DR. MILLER: Ms. Halloran?

MS. HALLORAN: Could you say more about your hair monitoring program, how big it is and how much does it cost?

DR. MIDDAUGH: We have just started this program, and the reason was to actually be able to try to provide ongoing surveillance evidence to document the validity of our dietary recommendations. There are around 12,000 live births in the State of Alaska. We just started the program in June. It is available to all women, free of charge to their provider to send their hair in to the state lab where it will be measured and the results will be reported back to the provider.

We believe that by doing so, one, we will be able to follow trends over time. Two, if we find any evidence of unexpectedly elevated levels in any geographic area, any village, any sub-targeted component of the State, then we can go out and do more detailed evaluations and investigations to try to determine why the hair levels are higher and, if necessary, we can always develop targeted advisories.

MS. HALLORAN: How much is this costing?

DR. MIDDAUGH: We are using Frontier Geosciences. Dr. Nicholas Bloom's lab is a consultant to our State

Health Department and has been for some time, but we are setting up to run mercury in our new state laboratory. So, we believe over the next six months we will be able to offer the mercury testing in our own state lab, not have to use a contractor. That will lower our cost, and we are estimating that as we gear up with the volume we anticipate we may get by with less than $50 a test for all associated costs.

DR. MILLER: Dr. Shannon?

DR. SHANNON: I have a question and a comment. My question relates to your discussion of increasing rates of diabetes and obesity. In fact, you showed a slide of the increasing rate of diabetes. It wasn't clear to me if you were relating that to changes in fish consumption or mercury exposure and exactly what point you were trying to make there.

DR. MIDDAUGH: Yes, very much so, there is a rich experience, well documented in Canada from 20 years ago when fish advisories were given in Quebec to the Ashkenazi, followed by complete abandonment of their subsistence intake of traditional foods. That led to tremendous community problems, and we are seeing tremendous problems in Alaska not just from mercury but also from other contaminants brought to Alaska from long-range atmospheric transportation, and then these tremendous warnings against

the dangers of the contaminants, and people are abandoning the use of their traditional foods, including fish consumption. In the larger context of Alaska, the values of both nutrition and the potentials for severe public health problems have been played out and are a great concern.

DR. SHANNON: I am still not sure I understood. You have clear evidence that the increased rate of diabetes and obesity is associated with decreased consumption of fish in Alaska?

DR. MIDDAUGH: We have anecdotal evidence to support that association. It is clearly not the only factor going on. There is a tremendous increase in life expectancy so all the chronic diseases are increasing. But we also did extensive autopsy studies of Alaskan natives, looking at the association of omega-3 fatty acids and atherosclerosis, in collaboration with University of Louisiana and Dr. Jack Strong's group. Fifteen years ago we showed that the amount of atherosclerosis among Alaskan natives was about half of that of non-natives and there was a strong association between the amount of atherosclerosis and omega-3 fatty acids measured in the coronary arteries and also in perirenal fat. Now heart disease is increasing and we have evidence from dietary surveys that the amount of consumption of subsistence foods is declining.

DR. SHANNON: You didn't present any of those data. Can you say a little bit more about that? How much is fish consumption declining in Alaska? How much has it declined over the last 10 to 15 years? I don't remember you saying anything.

DR. MIDDAUGH: We don't have good quantitative data. What we have are subsistence harvest records. Harvest records are not dietary consumption records, but we have numerous anecdotal reports from the physicians around Alaska, from our nurses in the villages and, of course, the whole issue of contaminants has been one of headlines in the papers routinely for the last eight to ten years.

DR. SHANNON: I have to push you on this. I think any good scientist would want more than anecdotal data that you think there have been important declines in consumption. Do those data not exist, or why hasn't that been investigated?

DR. MIDDAUGH: I mentioned that there are four major dietary survey projects that have been developed in the last several years, funded by ATSDR, EPA, NIH and CDC, and we are hoping that that information will provide some of the quantitative evidence that we can use to compare dietary consumption practices today versus the data that was accumulated 15 or 20 years ago by nutritionists with the Indian Health Service.

DR. SHANNON: Maybe I misinterpreted your introductory comment, but if I understood you to say that you thought that low level of mercury exposure may not have an effect, and if it does, it is subclinical and, therefore, probably unimportant and it isn't clearly irreversible, my comment would be that I don't think that the weight of scientific evidence that we have now would support those statements. Maybe that is not what you said.

DR. MIDDAUGH: Well, I would say that in Alaska, for example, we have the highest rate of fetal alcohol syndrome in the world and we have tremendous problems with infant mortality and nutrition and recent studies have documented borderline vitamin A and vitamin D deficiency among newborns and infants. We have very serious, well-documented, very significant public health problems and we believe that abandonment especially of fish consumption but also other traditional food consumption would cause a great public health tragedy among Alaskans.

DR. SHANNON: Right, but we are here to talk about mercury and the issue is whether mercury exposure is important or not and it just seemed like you minimized it. Again, my only comment is that I don't think that the weight of scientific evidence would support that.

DR. MIDDAUGH: I would only respond to that by saying that we are very concerned about mercury exposure in

Alaska. That is why we have developed some of these studies. That is why we launched the statewide monitoring program because our available evidence is suggesting that, at least in Alaska, our exposures are very low, far lower than we would have predicted based on consumption and fish species mercury level monitory data, and it is something that we intend to pursue with great vigor in the future.

DR. MILLER: Dr. Dwyer?

DR. DWYER: Thank you for a very interesting presentation, and I wanted to congratulate you for this monitoring program that you are putting in place.

The question I have is how will that work? It really isn't necessarily the people in Fairbanks and Anchorage that you are interested in. It is the people in the little, tiny towns that are very isolated and hard to get to. I know a former colleague and friend, Betsy Nobman, has done some of the studies that Dr. Shannon was asking about and I know how difficult it is to get food consumption data in some of those places. I wondered how you are going to get the samples of the hair and so forth in these remote villages that are very inaccessible in many cases.

DR. MIDDAUGH: Yes, actually Betsy Nobman is continuing to work on these dietary surveys that I have mentioned. Dr. Berner's infant cord blood study is based

on the rural hospital hubs to which pregnant women come in to deliver, and the Alaska Tribal Health Consortium in Anchorage has about 100 births per month, again, in many cases high risk pregnancies that are flown in from the villages. But the hair program is a component of Dr. Berner's study so it is located in those rural hospital areas. Then, should we find any evidence of elevated mercury, we can go out to the village and offer mercury testing not just to pregnant women but to women of childbearing age.

So, initially we focused on pregnant women, one, because they are of greatest concern for their own actual exposures and the fetal exposure, but also in terms of just the amount of money we have available to support the program. But the full intention is that should we find any elevated levels or higher levels than expected, then we can go back out to that area, the geographic area or to those villages, and do much more extensive testing and then liken that to detailed dietary exposure to determine if there is some unusual exposure or some unexpected elevated levels of mercury which we were unaware of, or for which a local advisory might be appropriate.

DR. MILLER: Other comments?

[No response]

Thank you. I have just been informed that Dr. Anderson will be arriving here at about one o'clock. The thunderstorms last night have prevented him from landing at Reagan. In order to accommodate this, I would like to change the agenda just slightly. I wonder, Dr. Lockwood, if you would mind making your presentation now, before the break? I understand you will just need about five or ten minutes.

American College of Obstetrics and Gynecology

DR. LOCKWOOD: Thank you. I am Charles Lockwood. I am an obstetrician and I was the former chair of the American College of Obstetricians and Gynecologists, Committee on Obstetrical Practice that acts sort of like a clearinghouse for information that is then disseminated to the 40,000 or so fellows in the College. Virtually all obstetricians and gynecologists in the United States are fellows in the college so it is relatively unique as a combination trade and educating society in medicine.

The mission, of course, of the American College of Obstetricians and Gynecologists is to improve the health care of women and their fetuses, and we are somewhat confused and very, very anxious to be able to communicate with our fellows and, through our fellows, our patients precisely what message should be given to them regarding

the safety of their food supply, and specifically the amount of fish that they can take in that is safe.

The College is concerned particularly because we have been urging patients to eat fish for the past ten years because there is evidence that it may improve health outcomes, reduce the risk of preeclampsia, perhaps affect premature labor and so forth. Although none of the literature is particularly robust, certainly the bulk of it suggests that fish intake may be beneficial.

We are also very concerned that there may be, as has been implied already today and I suspect discussed yesterday, significant variability in the content of mercury in fish among different regions. It is very nice that Alaska has such a low supply of mercury, and that is very good for the pregnant women in Alaska but we are very concerned about the other regions of the country that might have substantially higher contents of mercury and applying a uniform standard. This is sort of the federalist response to the Alaska statement, we are concerned that applying a single standard may, in fact, underestimate the risk to the newborn.

Although I certainly am very sensitive to the notion that different regions need to educate their people, our problem is that we can only communicate with our 40,000 obstetricians and that message has to be short, sweet,

clear and concise. It needs to be able to then be translated and given to their patients. If we rely on the states to do that, since there is substantial variability in their monitoring and also in their communication of the levels that might be elevated for mercury in different water sources, that is going to lead to complete chaos amongst obstetricians and gynecologists.

So, we do applaud the EPA and the FDA for giving us some guidelines and a fairly simple message to convey. However, having said that, we are concerned that, in fact, we don't know enough about the neurodevelopmental effects of mercury. The literature has been, at best, unconvincing. We would like to urge the NIH and other federal agencies to support research to establish in a much more precise and rigorous way what mercury does to the developing infant's brain. We would like fairly exhaustive studies done in primates and in vitro studies to assess the effects of mercury on nerve development, and so forth. In addition, we would like far more detailed epidemiological studies, coupled with child development studies, to be able to get some sense of whether there is at least a crude correlation between fetal in utero exposure to mercury and subsequent neurodevelopment and its effects. So, research I guess is the message there.

We would also like studies to establish whether or not mercury is teratogenic. It is pretty clear that in high concentrations it can induce fetopathy but it is not so clear that it causes birth defects and we would like to know that.

Finally, I guess we would urge that if you are planning to change the RfD that is used by the FDA that you do err on the side of being conservative, err on the side of, for example, accepting the Institute of Medicine's recommendations because we don't want to discover 15 years from now that, in fact, the level was too high and we have had an effect on the development of the next generation of our citizens. Thank you.

Questions of Clarification

DR. MILLER: Thank you. Any comments or questions? Yes, Dr. Nordgren?

DR. NORDGREN: Dr. Lockwood, your organization is in the front lines on this issue, and I think it sounds like your organization has very carefully studied the issue that we are all facing here. My question to you, and the reason I am asking this question is, dealing with fetal alcohol syndrome in the past, I think many obstetricians were way behind the eight ball as far as recommendations in their practice as to good scientific knowledge. My question is do you think within your organization this

information is filtering down? That is a hard question to answer.

DR. LOCKWOOD: It is a hard question to answer. The life of an obstetrician is difficult. We have really added substantially to the burden of information that we have to convey to our patients. Some of that is actually regulated by states and some of it has, in a sense, been de facto regulation by the College endorsing certain programs and policies, for example, cystic fibrosis screening and universal HIV screening, and so forth so that a substantial amount of time is spent by the average obstetrician counseling patients.

So, if you are attempting to pay your $115,000 a year malpractice premium, as you would in Long Island for example, and you are attempting to support your staff and so forth, and increasingly large staff since more and more counseling is done by nurses, etc., and you are facing a 50 percent reduction in the average reimbursement of your services by managed care organizations, which we have over the past ten years, and, therefore, you are forced to see many more patients in a shorter period of time, it becomes increasingly more difficult to add to the burden of information in the time that is available.

This is not to say that we don't have an obligation to do the very best we can with every patient,

but from a practical perspective, there is only so much we can do; there is only so much information we can convey and at some point this all becomes crippling. You know, I live in a lovely Ivy League world with plenty of time to spend with every patient and, yet, even for me it is becoming incredibly difficult to give all the information that we have. We have to talk about exercise. We have to talk about vaccinations. We have to talk about infectious disease exposure. We have to talk about screening for aneuploidy or Down's syndrome. Now we have to talk about cystic fibrosis screening; a variety of other ethnic specific genetic disorders, and on, and on, and on.

So, to be able to convey the complexity of these issues to the average pregnant woman is impossible. It can't be done. We can provide educational resources. We can provide information on web sites. We can have patient handouts, and we are more than happy to do all that, but we do need a very simple, clear message to our patients and I think that the College was happy to pass on the information that the EPA and the FDA produced but we understand that, in fact, that may be a fairly--depending on your political perspective--conservative or liberal recommendation. So, we will follow whatever the recommendations are, but our bias would be that those recommendations be as conservative

as possible from the perspective of the developing fetus. I hope that answers your question.

DR. MILLER: Dr. Lee?

DR. LEE: I was just following up on a casual mention you just made. Is there a single source or clearinghouse of information for pregnant women to go to for recommendations on prenatal care and diet? Do you point them to a particular site, or do you have just a whole array of brochures?

DR. LOCKWOOD: The bible for provision of prenatal care, if you will, is contained in "Guidelines for Prenatal Care," the fifth edition of which is about to come out. Having helped write that, I am embarrassed to say that I don't believe we incorporated any recommendations about mercury. There may be time, and I will work on that right away to be able to do that. It would be nice, of course, if you changed your recommendations you would do that in the next 25 minutes so I would be able to do that--

[Laughter]

The second line of information, and the one that is much more time sensitive is the Committee opinion which is rendered by the Committee on Obstetrical Practice and that is distributed via publication in the Journal of Obstetrics and Gynecology to virtually all of the fellows of the College. Rarely will we actually do direct mailing.

For example, if tomorrow the New England Journal of Medicine pointed out that exposures of mercury are substantially higher than the current recommendations would allow caused neurodevelopmental abnormalities, we would send a Committee opinion and literally mail it to every single member of the College with new recommendations. So, we can effect rapid change and those opinions are looked at very carefully because they are construed by our trial lawyer colleagues--I hope none of them are in the room--as the standard of care in the United States.

DR. LEE: That is a very good mechanism for communicating directly with your members, but is there any attempt to communicate directly with your patients?

DR. LOCKWOOD: We do assume that physicians speak to their patients, particularly if the topic is critically important. But, in addition, there are handouts that are available that are published by the College that most obstetricians and gynecologies have in their office. So, if there is a new recommendation that is going to be made, we could certainly incorporate that into the general educational efforts the College makes directly to patients.

DR. MILLER: Dr. Dwyer?

DR. DWYER: I just wondered, given the current state of information we have available, what do you intend

to put in the ACOG handbook? What is the one-liner that you want your ACOG members to have?

DR. LOCKWOOD: We would put in the "Guidelines for Prenatal Care" what we already put into our general publication. There is yet a third layer of communication and that is a newsletter that goes out to all of our fellows, and we have already put in that newsletter the recommendations of the EPA and the FDA regarding the amount of fish to eat and the various other aspects of whether, you know, it was commercially obtained.

DR. DWYER: But do you really expect an obstetrician to have enough time to go through all of that? I mean, what would be the one-liner?

DR. LOCKWOOD: Yes, these are one-liners. Most obstetricians do read that. Whether they incorporate it into their practice is up to them. We don't have any way of monitoring at this point what obstetricians actually tell their patients in their offices.

DR. MILLER: Dr. Acholonu?

DR. ACHOLONU: Thank you. I have a very similar question to Dr. Dwyer's. You made a statement, and please correct me if I have put it down wrongly, that we don't know enough about the neurodevelopmental effects of mercury. I have been sitting here, listening to summaries and reading about the Faroe Islands Study and the

Seychelles study. What is the ACOG opinion of those studies?

DR. LOCKWOOD: We certainly understand, based on the exposures that occurred in the Minamata Bay, what substantial exposure would do to the developing fetus, and that the manifestations of cerebral palsy and major retardation and the other various neurodevelopmental abnormalities that occurred in response to that exposure are pretty straightforward. I don't think there is much debate about that. The thresholds that have been calculated on the basis of those exposures I think are robust and no one is going to dispute them.

Reviewing the data from the Faroe Islands and the Seychelles Islands, as well as the New Zealand study leaves us a little bit more lost. It is unclear whether or not you can set a specific exposure level that would be safe and, conversely, one that would represent the lower limit of absolute risk. It is unclear, sort of like the fetal alcohol story, whether there is an absolute discrete threshold below which there is no risk to neural development, or whether this is a continuous exposure.

I think we would like to see literally a dose response study and, if you will, a time course study to inform the recommendations that you all are going to be making. But I don't see at this point, based on the

information that I have been given, that you can say that a certain level is safe or that a certain level is absolutely unsafe. In general, what we have ended up doing with fetal alcohol is to say that we are not sure that any level of alcohol intake by a pregnant woman is safe. Most obstetricians will say it is okay to have a glass of wine once a week or so and it probably is okay but, in fact, since we never could establish an absolute limit to alcohol exposure that could be deemed safe we general proscribe the use of alcohol in pregnancy.

I suppose at this point, if we are left with increasingly concerning information about the lack of a lower limit of mercury exposure, pregnant women will stop eating fish, but there are a lot of health benefits to eating fish and it is a relatively cheap source of protein. There may be some additional benefits of reducing oxidative stress that might induce preeclampsia or per-term delivery; may affect fetal growth restriction by impairing placentation. So, there are a lot of reasons to think that fish might be useful for pregnant women to take in but apparently, if we want to be absolutely safe, we have to tell them that they have to go to Alaska and eat fish with very low levels of mercury.

DR. ACHOLONU: I think you have answered most of my questions, but did I understand you to advocate that NIH

and other groups should give research grants to your organization or to other people do to research on the effect of mercury on the developing fetus? Is it to your organization?

DR. LOCKWOOD: Not through our organization, we don't conduct original research. It would be up to the appropriate academic medical center to do that. But, yes, I think we need to have more research on the topic.

DR. ACHOLONU: Do you have any more areas where you want the research to be concentrated because a lot of work has been done on the effect of mercury on children and prenatal effects? What area of research do you want this thing to be concentrated on?

DR. LOCKWOOD: We would like a body of research that informs our counseling about fetal alcohol syndrome, which is a substantial amount of research, done in animal models and in humans, with long-term follow-ups, and an enormous effort made to understand precisely what the effects of fetal alcohol exposure were. I don't think there is anywhere near the quantity or quality of research that was done in that area in this area.

Now, in a world of limited resources that may not be a reasonable expectation, particularly if the stock market goes down again today. But, in fact, I and the rest of our Committee and the rest of the College's leadership

is not convinced that the information that is available is adequate.

DR. MILLER: Ms. Halloran?

MS. HALLORAN: Some women in the United States don't get prenatal care from a physician. Do you have any advice on how to get this message to those women?

DR. LOCKWOOD: Well, there are several reasons women don't get prenatal care. One rare reason might be physical access. That might be a bigger issue in Alaska. But, generally speaking, people who don't seek prenatal care are less likely to be responsive to messages about the health of their fetus or behaviors that should be avoided that might impair the health of their fetus. So, I would wonder right off the bat whether whatever I recommend or am about to recommend would be cost effective in that particular group of patients. That is a real dilemma with fetal alcohol syndrome, drug abuse and a whole variety of other exposures.

But it is a little hard for me to imagine that that population can be easily accessed and that that information could be easily conveyed or be readily accepted. There are issues with language barriers, and there are issues with poverty and crime, and many other things.

The March of Dimes has been very, very effective I think in spreading the message that folic acid supplementation is something that should be begun by women of all childbearing ages. There is evidence that the amount of folic acid used in women who are anticipating being pregnant has increased substantially, and I think if a solid recommendation comes out of this body and it is based on good scientific evidence and everybody can get their hands around it, and feels comfortable with it, the March of Dimes would be an excellent organization to help disseminate that information, provided, of course, that they also were comfortable with the content. But they seem to do a much better job at reaching everybody than we do as physicians.

DR. MILLER: Dr. Nordgren?

DR. NORDGREN: I would just like to follow-up on Dr. Lee's question. I don't think you really answered his question. You didn't say your organization has a consumer web site like, for instance, the Academy of Neurology that has a web site so that people who want information about neurologic disorders can go to. Your organization doesn't have such a thing?

DR. LOCKWOOD: We do. We do have a web site that consumers can access and there is patient information there.

DR. MILLER: Dr. Friedman?

DR. FRIEDMAN: I just want to make a little comment about the research that you are advocating. I am from the National Institute of Child Health and Human Development, and I will take the message back, but most of the research that NIH supports is investigator initiated research. So, I think the word needs to go out to researchers in your community to ask those questions and through submitting publications.

DR. LOCKWOOD: An RFA would help.

DR. FRIEDMAN: Okay, I will pass on the word.

DR. MILLER: Dr. Fischer?

DR. FISCHER: Dr. Lockwood, I would like to ask whether you think that the fellows in the College would support and participate in a national monitoring program for mercury exposure. To do that would require a lot of effort from a lot of people, I suppose, including those in your organization. Do you think that that would be possible?

DR. LOCKWOOD: I think not only would it be possible, but there would be great enthusiasm for it. I was very intrigued by what Alaska is doing. I think that sort of cuts to the chase and gives us a lot of valuable information. Speaking for my organization, I don't know what my bosses are going to say but I would say that that

would be something we would enthusiastically embrace. You know, if we had envelopes and we could snip some hair and it was relatively a straightforward process, I think we would be happy to contribute to that.

DR. KUZMINSKI: I have one more question.

DR. MILLER: Go ahead.

DR. KUZMINSKI: I would just like to return, Dr. Lockwood, to the question asked earlier. Perhaps you could give us an example from another area of a message that works for your fellows in the College. You mentioned that you put in the EPA and the FDA recommendations on fish consumption. We have had discussion here that one person reading all of those messages together might get confused. So, as a guidance to this committee, can you give us the one-liner that has been referred to from another area of advice that gynecologists or obstetricians give to their patients?

DR. LOCKWOOD: As an example, I think folic acid is a good one. We recommend that all pregnant women take a milligram of folic acid. We recommend that, in fact, you begin the consumption of folic acid really during your childbearing years and certainly if you anticipate being pregnant in the near future since folic acid reduces the risk of neural tube defects only if the exposure occurred prior to the development of neurulation in the embryo.

That is a message that seems to be working. The prevalence of neural tube defects is dropping. Enrichment of the food supply may have helped as well, but it is clear that most pregnant women currently begin folic acid supplementation prior to conception. So, there is an intervention that works. It is cost effective. It has reduced a really terrible birth defect, and it is done in a way that doesn't invoke abortion or other things that society doesn't like to discuss.

DR. MILLER: Thank you very much, Dr. Lockwood. We are going to have a break now. Would you please return in 20 minutes? That makes it 11:05. Thank you.

[Brief recess]

DR. MILLER: Before we go to the next speaker, an issue has come up. Over the last two days we have been receiving enormous amounts of information with sets of numbers derived from different sources, and so on, and Dr. Kuzminski has a recommendation which I think we would follow in order to clarify some of this.

DR. KUZMINSKI: Thanks for bringing it up, Dr. Miller. I am just reflecting a little session three or four of us had after Dr. Miller adjourned us yesterday afternoon, but I know I certainly, personally, would find it helpful as part of the total information flow if I had in front of me--and perhaps the rest of the committee would

find it helpful too--something that we could get from the FDA on one piece of paper, the various levels--we hear 0.1, 0.3, 0.4 from the various sources and agencies, sources for those numbers--how that translates into blood level mercury; how that translates to hair level mercury; how that translates to consumption of perhaps high level fish, low level fish, medium level fish. Again, just as a piece of information, one part of the jigsaw puzzle as I mentioned yesterday, of the total information flow to help us have deliberations.

As I keep going back to the five questions that the agency has posed to us, the charge and the questions, I think that one-page summary would be helpful. I have been making notes. I am not sure that they are correct and I just want to avoid any chance of error.

DR. MILLER: What I am going to do is to ask the secretariat to get together with our FDA colleagues and provide us with as much of that information as they can, and get this distributed to the committee before tomorrow. Yes, Robert?

DR. RUSSELL: Included in that, there was a translation being made between parts per million of fish and the 0.1, 0.3, 0.4. I would like to see that as part of the column as well. By the way, it was never explained

exactly how that is transformed, parts per million into 0.1 ug/kg/day.

DR. MILLER: I think it was based on consumption.

DR. RUSSELL: Assuming 8 oz, a half a pound of fish per serving?

DR. MILLER: Well, that ought to be specified.

DR. RUSSELL: Yes, that is what I would like to see, if we could.

DR. BOLGER: Since I am the one who is going to have to do this, I want to make sure I understand what you want. I mean, I understand how this gets terribly confusing because you have these different terms that are used and it is unclear what they really mean, but they are really different terms for the same thing. So, I am trying to get a handle on what it is you want. I mean, trying to translate an ADI, MRL, RfD, TDI, whatever you want to call it, those are all different terms for the same thing. They are safe levels of exposure.

The FDA's ADI is really not relevant for this consideration because the ADI was based on the adult endpoint; it was not based on the fetal endpoint and was never part of the consideration of this advisory because the advisory is focused on fetal sensitivity. So, that is really not germane. The TDI WHO is also based on the adult

endpoint; it is not based on fetal. So, that too is not germane to the advisory.

Translating a dose level, a safe dose level to a concentration in fish is all predicated on what residue level you use in the fish and what level of consumption you use to derive an estimated exposure.

DR. MILLER: I think that this will take a real long time and should be helpful, not confusing. Can I suggest that you and Larry Kuzminski get together for a couple of minutes and see if you can clarify what it is.

DR. BOLGER: Right, so I have a clear idea of what it is they want.

DR. KUZMINSKI: I would be glad to do that, but I would invite anyone else on the committee to join us.

DR. MILLER: I don't want you to run out now.

DR. BOLGER: Well, can I leave?

[Laughter]

DR. MILLER: You not only can leave; you have to leave. Our next speaker is Dr. Diana Zuckerman, of the NCPR, to talk about their recommendations.

National Center for Policy Research for Women and Families

DR. ZUCKERMAN: Thank you very much. I am Dr. Diana Zuckerman. I am president of the National Center for Policy Research for Women and Families. I am really

delighted to be here and I thank you for inviting me to speak.

CPR for Women and Families is a nonpartisan, nonprofit organization that reviews scientific and medical research, and explains the implications of that research for public policy and for the health and well being of women, children and families. Our mission is to ensure that research information is made available and understandable for policy makers and the public, to support policies that benefit public health, and to help ensure that consumers can make educated choices.

Just as an aside, my own training is in epidemiology and psychology, and my policy perspective comes from working in the House of Representatives, the Senate, briefly the White House and, most recently, working for and with many nonprofit organizations that are very focused on consumer issues. This is a combination that doesn't come in too handy very often, but I think might actually be the right combination for what I am going to talk about today.

Our Center is very concerned about methylmercury exposure, especially for children and pregnant women. We believe that the Food and Drug Administration's current efforts at protecting the American public from the health risks of methylmercury are not adequate to protect the

public or to educate them so that they can protect themselves.

We are concerned because the FDA does not adequately monitor methylmercury levels in commercial fish supplies. These levels may change over time but the FDA does not collect data to determine if that is true so we think surveillance is really essential and needs to be improved.

We are concerned because the current FDA advisory is incomplete. The advisory should be revised to include information about tuna. Although the levels of methylmercury in tuna, and especially canned tuna, are lower than in other fish that are included in the current advisory, the amount of tuna consumed is typically so much higher that a public health perspective requires that the FDA widely disseminate risk information about fresh tuna and canned tuna.

Our third main point is that we are concerned because FDA's dissemination of information about methylmercury exposure has not reached most consumers. Even health-conscious consumers are unaware of the overall risks of methylmercury in fish and they don't know which fish pose the greatest problems.

More than a year and a half ago I attended a small meeting with Joe Levitt and other consumer groups to

talk about FDA's plans regarding methylmercury advisory. It was really an excellent meeting and the major focus of the discussion, as I recall it, was whether the FDA should include information about canned tuna in their advisory. It seemed to be already assumed that fresh tuna would be included.

Most of the consumer groups strongly urged that canned tuna be included in the advisory and we spent a lot of time talking about how to make that information available to consumers; what do you need to do to make sure that consumers know not just about tuna but about all the fish involved in the advisory. We talked about the need to have labels on food that is sold in supermarkets and fish markets, and also about the need for information on restaurant menus.

So, I was certainly very disappointed and actually extremely surprised when the advisory came out and it didn't mention tuna at all, and very disappointed at the lack of dissemination of information once the advisory came out.

It seemed to us that FDA was making little or no effort to inform consumers of these risks at the time when it would do the most good, which is when they are buying fish when they are in the market, in the supermarket or ordering it in a restaurant.

Based on the National Academy of Sciences report, we are convinced that the FDA should be doing more to protect vulnerable populations, as you know, pregnant women, women who might become pregnant, nursing mothers and young children. In our experience, the National Academy of Sciences is actually pretty cautious. So, when they suggest that 60,000 newborns each year might be at risk for neurological problems due to methylmercury we take that estimate very seriously even though we understand very clearly that it is just an estimate.

Given my training in epidemiology, I am really very interested in data and I strongly believe that we need better data, and it would certainly be preferable to be making these kinds of decisions based on better data. The American public relies on the FDA to require or to collect data so that we will better understand the risks of exposure, in this case exposure to methylmercury in the fish that we eat or the fish that we want to eat.

It seems to me that the epidemiological research suggests that methylmercury in fish can potentially pose very serious problems especially, of course, in the developing fetus. But there are two ways to be exposed to this. One would be to consume fish that are high in methylmercury. That is what is in the advisory right now. But what is less understood is what happens when women

consume large amounts of fish that have moderate amounts of methylmercury, fish like tuna.

My feeling is this is not rocket science. We can get just as overweight from eating lots of light ice cream as we can from eating a smaller amount of Haagen-Dazs. So, it is an issue of not just which fish but how much fish people are consuming and, obviously, tuna is a popular fish.

We believe tuna should be included in the advisory because Americans eat a lot of tuna and American women eat a lot of tuna, both canned tuna and fresh tuna. We looked at the government data that you all have in your book. We looked at even the U.S. Tuna Foundation's estimates that the one percent of women that eat the most tuna eat almost 7 oz a week. Then, there were other estimates that were for 8 oz or more. Then we were wondering what about the top half of one percent, how much tuna are they consuming? That is still a lot of women in this country that are being exposed to potentially harmful levels.

Canned tuna is a convenience food because you can buy it now and eat it almost any time, and because almost anybody in the United States can afford it. Just last week, the CVS stores offered cans of brand-name tuna for 44 cents a can. There just aren't that many main courses in

America that you can buy for that amount of money. Most of them, including other favorites for children like hot dogs and bologna, are perceived to be rather unhealthy. So, this makes canned tuna especially appealing to low income women, including pregnant women and the mothers of young children.

If you believe, as we do, that an FDA advisory should reflect the science, then I think you will agree that a very popular fish such as tuna needs to be included in the advisory. If scientists at the FDA believe that the level of methylmercury in canned tuna is not sufficient to warrant being included in the advisory, it seems to us they need to prove that. They need to prove it by providing current data. It is not enough to say that the evidence is unclear; they need to collect the evidence that will either support or refute those concerns.

The current FDA advisory is entitled, quote, an important message for pregnant women and women of childbearing age who may become pregnant about the risks of mercury in fish. At the bottom of the page it mentions, almost casually, that, quote, it is prudent for nursing mothers and young children not to eat these fish as well. I think it is obvious that those warnings deserve more attention than they have in the current advisory.

We all know that most foods have risks and benefits. We know that cheese provides calcium, but it can also be high in fat. Juices can provide vitamins, but pediatricians warn parents of young children to limit their juice consumption. So, it makes sense to us to include both sides of the issues, the benefits and the risks, for fish as well in an advisory and in any kind of information that is being disseminated. But we also share your concerns that it is difficult to do this succinctly and in ways that consumers can understand.

So, we think that it is important what is in the advisory, but also how that information is disseminated to the general public. Obviously, the advisory needs to reach more people. For example, how many people know that the FDA believes that pregnant women and women who might become pregnant should limit their consumption of cooked, store-bought fish to an average of 12 oz a week? I would have to say I have asked several health-conscious, fish-eating types of people and none of them were aware of it. In fact, I asked a pediatrician who teaches at a major university and is active in the American Academy of Pediatrics, a man who does not eat red meat and considers himself very health-conscious, and happens to be married to me, and--

[Laughter]

--he barely knew what methylmercury is, and he certainly knew nothing about the 12 oz limit for pregnant women.

What efforts has the FDA or the fish industry made to get information from the FDA advisory into women's magazines, parenting magazines, or other publications that are read by women of reproductive age? Why not have PSAs on TV talking about this issue? Because if they are on TV, they are going to reach a lot more women than anything else that the FDA could possibly do.

Since the FDA advisory states that fish consumption should be limited to an average of 12 oz per week for pregnant women and women who might become pregnant, why not place that information directly on menus and all fish products that are sold, including canned tuna? Well, I think we know why not. This is a very controversial issue. But we can't let public policy be dictated by concerns about controversy.

In the absence of complete information about methylmercury contamination of fish, we believe that the FDA should warn vulnerable populations not to eat swordfish, shark, king mackerel, tile fish and fresh tuna since they have previously been shown to contain unsafe levels of methylmercury.

We believe that the risks outweigh the potential benefits since at risk consumers can simply switch from eating one kind of fish to another kind of fish. Fish are healthy but there are many different kinds of choices of fish. We also believe that consumers should be advised to limit their consumption of canned tuna.

We realize that companies are concerned that people will stop eating tuna, particularly canned tuna, if there was such an advisory. I looked at the data from the focus groups that was on the CD disc that you all received, and obviously those focus groups were quite persuasive in saying we want simple information--is the fish good or bad? We want to know which fish are good. We want to know which are bad and we want to not eat the ones that are bad.

But as somebody who has worked on research for a long time, and those of you who have know focus groups are not necessarily the best source of information about what people actually do in their real lives, particularly when a focus group is first given information that might be shocking or disturbing, they are likely to respond in a more radical way than they would as time goes on.

Let's face it, millions of Americans still eat hot dogs despite warnings about nitrites, and remember when there was a time when it seemed like nobody was ever going to eat a hot dog again. We eat processed foods despite

warnings about salt content. We still eat fresh fruits and vegetables, not as many as we should, despite warnings about pesticides.

I think there would be an initial shock if there were labels on food and it would probably result in lowered consumption for a short period of time, but over time people learn--they will learn with fish, just as they have learned with other food products, that moderation is the key; that there are certain foods that might not be for pregnant women but that doesn't mean that other people can't eat them, and that there are certain foods where the levels are such that eating in moderation is important and they shouldn't overdo it. We certainly managed to get that message out on a lot of other foods, whether it is ice cream or alcoholic beverages or cakes or cookies, otherwise our kids would be eating nothing but cakes and cookies I think. So, there is no reason to think that in the same way that we teach people about moderation in all kinds of foods we can't teach them that about canned tuna.

DR. MILLER: Five minutes.

DR. ZUCKERMAN: Five minutes? Fine. When consumers purchase swordfish, shark, king mackerel, tile fish and fresh tuna that is either prepackaged or packaged at a fish counter, we believe the package should bear a label that tells pregnant women, women who might become

pregnant, nursing mothers and young children not to eat it. At restaurants, a similar warning should be on menus if those items are served.

Labels are also needed for canned tuna, and we urge that the FDA advise vulnerable populations to consume canned tuna infrequently until a more comprehensive analysis of the methylmercury content of canned tuna can be performed that is more reassuring than the information we have now. Obviously, we think that analysis should be done as soon as possible.

Our recommendations are consistent with the precedents that have been set to provide clear warnings for pregnant women and children, even in the absence of data establishing a specific risk. I think the most obvious example would be the warnings on alcoholic beverages. There are warnings on every alcoholic beverage that pregnant women should not consume them, even though there really are not data that support the idea that no pregnant women should ever drink any alcoholic beverage.

My final brief remark has to do with regulatory standards. We urge the FDA to set a regulatory limit that is consistent with the EPA standard since that has been scientifically justifiable for the protection of public health according to the National Academy of Sciences. We strongly believe the FDA should monitor the levels of

methylmercury in shark, swordfish, king mackerel, tile fish and fresh and canned tuna, and if problems arise and with this monitoring they find that the levels are higher than expected, we believe that those fish should be removed from the market.

Thanks very much for the opportunity to speak with you today, and I am happy to answer any questions.

Questions of Clarification

DR. MILLER: Thank you. Comments or questions? Dr. Dwyer?

DR. DWYER: I wonder if you know of any advisories in Scandinavia or other countries that have taken actions on this, and the effectiveness of those advisories.

DR. ZUCKERMAN: I am not familiar with that. You know, I don't have that information. We do know that there are all kinds of advisories but people get a lot of their information from the media, and I think it is very unfortunate that the FDA across the board does not make better use of the media in getting the word out on a wide variety of issues but, in this particular case, I think, you know, people do care about what they eat and I think that magazines and newspapers and TV would care about this.

It is a little scary working with the media on issues like this because you are so afraid you are going to

get these extreme headlines and these very extreme statements so you just have to keep at it until the message comes out that is accurate. I am not saying that is easy, but I am saying it is possible, and I also have no doubt that the folks who sell these products will do their very best to promote them and that will counterbalance the warnings. So, I think that we can get to a point where consumers are reasonably educated. They are not going to perhaps understand all the nuances, but they will be reasonably educated and will be able to make reasonable choices and we will have provided information to enable them to do that.

DR. APOSHIAN: Ten years ago our laboratory did a study at the University of Arizona where we studied students as far as the urinary mercury was concerned for, I think, it was a 24-hour period. When we got the results in we had three outliers, about ten percent at least, maybe a little more. An outlier is always a problem. You want to know why.

So, when I talked with each of these outliers, and they happened to be women, young college women, I asked them what they had had for dinner or lunch, what they had eaten because part of receiving their honorarium was signing something that said they had not eaten seafood for a week. That was spelled out, seafood. Each of them said

they had had a can of tuna fish for lunch. And, I said, "how could you do that? You accepted our honorarium; you signed an agreement." And, they said, "we just didn't think of tuna as seafood."

Now, in much of the literature that we have, they talk about swordfish and they talk about fish, and when I did my little survey on how much mercury was in tuna fish cans, I went to each can of tuna fish sold at the supermarkets in Tucson and nowhere does the word "fish" appear on a can of tuna. My wife, when I talked this over with her, and I should even mention this, my wife, who is a 40-year collaborator of mine, said "everyone knows that tuna is fish." But I wonder with the educational level in our country--

[Laughter]

--how many people really know that tuna is fish, and I would really like to suggest that it is very easy for a company to put the word "fish" on a can of tuna. I think that there is a real need for education, as I am sure you all realize, for this whole problem of mercury in all kinds of fish.

DR. MILLER: I hope that that experience doesn't reflect the quality of your students--

[Laughter]

DR. APOSHIAN: I must say that one of these young women was a graduate student, a year away from her Ph.D. and she is now a department head of the leading biotech company in the world, a very educated woman.

DR. ZUCKERMAN: I know you didn't exactly have this question but I do want to follow-up on the issue of outliers because I think it is really important. I will admit to something that I probably never said to anyone in my life, and that is that when I started graduate school I only knew how to make four things pretty much, hamburgers, hot dogs, tuna noodle casserole and tuna salad. So, there are people who eat a lot of certain foods, particularly students who are certainly of reproductive age. So, there are outliers out there and we have to care about the outliers and if we don't have warnings that warn those outliers, there are people who can be harmed.

DR. MILLER: It just occurs to me, as we were talking before, I think the real problem is to translate knowledge into action, and that is where the hard thing comes because very often from a number of studies that have been done over the years, people, particularly students, can be extremely knowledgeable about the subject but their behaviors are unchanged. I don't know the solution to that problem; I am not sure anybody does.

DR. ZUCKERMAN: Yes, I agree but I guess I don't think it is the role of the FDA or even the responsibility of the FDA to do that. I think it is the role of the FDA and the responsibility of the FDA to make products safer by regulating and to get information so consumers can make the right choices. I think the FDA should do everything it can to make that information available in a way that people can use, but ultimately it is our decision. We make a lot of foolish choices in how we eat and how we live our lives, but it shouldn't be based on lack of information.

DR. MILLER: Other comments or questions? Yes?

DR. HOTCHKISS: FDA has in its arsenal of public health tools a number of avenues that it can pursue, along with what at least are naturally occurring or adventitious toxicants--one could take aflatoxin, for example, that FDA has chosen to take regulatory action for above a certain limit--rather than the way it has chosen methylmercury which is more to try to advise consumers about the safety or lack of safety. What would your organization's opinion be about what choice FDA has made in the case of methylmercury? Would you rather see something more along other adventitious toxicants, lead for example, or do you think they have chosen the right path in terms of warnings to consumers?

DR. ZUCKERMAN: I am not sure I understand the question. I will answer the best I can, and please follow-up if I miss the point here. Obviously, we think that first of all you deal with advising consumers. We also think that the regulation has been inadequate. We think that there is more information needed and more action needed if the information provides clear concerns about toxicity levels.

I guess the bottom line is it is not enough to have a two-page piece of paper that says this is what the FDA believes, and the FDA did have something in their magazine that has nice illustrations but, still, I think it is clearly at the college level, college reading level and, anyway, who reads that? So, I think that the FDA has really not gotten the word out. I mean, people do know a lot more about lead, for example, and it is much more rigorously regulated in a variety of ways but I think some of those are state and local decisions, I believe, not just FDA decisions. I don't know if I am responding adequately.

DR. HOTCHKISS: I think you are but let me be more specific. In the case of lead, for many years FDA had a very rigorous research program and in the days when there was lead used in manufacture of cans, rather than going out and telling select groups of consumers at large to limit their consumption of certain canned foods that they knew

would be high in lead, they chose to regulate product and not try to have the consumer self-regulate. They could do that, I presume, in the case of methylmercury and I was just wondering about your opinion about whether they should take that approach or the current approach.

DR. ZUCKERMAN: Sure, I agree. I mean, the preference would be to regulate the product and make it safer. I guess there are situations where a product can be safe for most people but not be safe for pregnant women or nursing women for example. Certainly, FDA has gone in the direction of putting a lot of responsibility on the consumers. Our organization feels they have gone too far in that direction, and I guess this is just one example of it where, yes, it is nice for consumers to have choices, but in this country people believe that the FDA makes sure that products are safe. So, no matter what you tell them, there is this underlying belief I think that if this product is being sold in my supermarket it is safe, and if these pills are being sold in my drug store, they are safe but, unfortunately, that is not always the case because they can be safe for some people and not others.

So, I agree that the FDA should be doing more to regulate the product, but if there are reasons why certain products can be healthy and good for many people but not for pregnant women, then I think it is okay to have warning

labels but they have to be really clear ones so that pregnant women, nursing mothers and mothers of young children know that.

DR. MILLER: Dr. Friedman?

DR. FRIEDMAN: I want to ask you to help me resolve a cognitive dissonance. Okay? You were emphasizing the importance of more research surveillance data and for more information about the connection between exposure and fetal development and infant development. So, you are saying there isn't enough knowledge out there about the ill effects. On the other hand, you are speaking with great enthusiasm about enforcing regulations maybe or advisories that are much more stringent than the ones that are out there, and making it more known to greater segments of the population. So, how does this fit together?

DR. ZUCKERMAN: That is a fair question. Let me clarify, my concern about surveillance is actually not so much about lack of epidemiologic research. I mean, there is epidemiologic research; it is progressing. There is some, I think, very clear data that methylmercury exposure is dangerous to children, to fetal development under certain conditions. What we don't know is exactly what conditions. But I think it is very clear that it is dangerous.

So, when I was talking about surveillance I was really talking about the levels in fish, current levels in fish. I think that a lot of the data are based on older information and we need current information. So, when I was talking about surveillance, that is actually what I meant.

DR. FRIEDMAN: So, you think there is enough in the mixed literature that exists now to warrant the recommendations that you made?

DR. ZUCKERMAN: Yes. I mean, I would personally like better data. I don't want to say that I think the data we have is adequate. You know, I am a researcher by training and I always want more data. But I think that there is enough. I think the previous speaker said something about erring on the side of caution and I think there is every reason to err on the side of caution in a situation where there are other alternatives that pregnant women can eat. You know, if this was the only fish available and fish was so great nutritionally for other reasons, that would be different. But there are other fish available.

DR. MILLER: Any other comments or questions?

[No response]

Thank you.

DR. ZUCKERMAN: Thanks very much. I have copies of my statement which I can leave.

DR. MILLER: We are now supposed to break for lunch. We are scheduled to come back at 1:30. I would ask you, if you would, to come back about one o'clock because we would like to get Dr. Anderson in this afternoon and we need to make up some time in that respect. Thank you, all, very much.

[Whereupon, at 11:45 a.m., the proceedings were adjourned for lunch, to reconvene at 1:00 p.m.]

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

DR. MILLER: We are ready to start the afternoon session. I want to remind the speakers that it is important that they keep exactly to their time so everybody has a fair shake at making their presentations. I will provide a five-minute warning before the end of their time. The first speaker this afternoon is Mr. Richard Wiles and Ms. Jane Houlihan. Ms. Houlihan instructed me to point out she doesn't have a doctorate and she didn't want me to continue calling her doctor. I want you to understand it was her idea, not mine.

Environmental Working Group

MR. WILES: Thank you. I am just going to read a little statement and then Jane will make the bulk of the technical presentation. My goal is just to give you the goals of our presentation and our ongoing work on mercury.

I am Richard Wiles. I am senior vice president of the Environmental Working Group. EWG is a nonprofit environmental research advocacy group, with offices in Washington, D.C. and Oakland, California. We are entirely foundation funded. We have no members and accept no money from industry or government.

EWG has a long track record in working with the pesticide program at the U.S. EPA on issues directly

relevant to the issue before the committee today. We have developed and presented two probabilistic exposure models to the EPA scientific advisory panel, one for acute exposure to organic phosphate insecticides and another for chronic exposure to arsenic by arsenic-treated lumber. Both of these models were embraced by the EPA and have formed the basis for significant changes in the way that EPA assesses exposure and risk to these types of substances.

The acute exposure model for OP insecticides is particularly relevant to today's discussion. This model has moved EPA away from regulating pesticides on the basis of average exposures or even fixed point statistical estimates such as the 98th percentile to risk assessment methods and regulatory policies for non-cancer health risks, such as those we are dealing with today, that are designed to identify and predict, in EPA's case, at least 99.9 percent of the most vulnerable population.

We are deeply troubled by the FDA's antiquated exposure and risk assessment model for methylmercury, and the fact that these models and methods have produced a mercury health advisory for pregnant women that allows thousands of unborn children to be exposed to unsafe mercury levels each year.

But let me be clear. We are not asking the FDA to adopt our model per se any more than they should adopt the models of the seafood industry per se. What we are saying is that the FDA needs to conduct its own probabilistic risk assessment through a public and transparent process and issue a comprehensive list of fish that women should avoid during pregnancy and, equally important, and I want to emphasize this and I am going to emphasize it over and over again, a list of fish that are low in mercury and high in omega fatty acids that women should eat more of during pregnancy.

The charge to the committee was to determine whether the agency's consumer public health advisory on methylmercury is adequate to protect the health of those who follow that advice. That is a quote from the charge. Our 2001 report, "Brain Food," addressed this question exactly and found, without question, that the current advice is not safe for those who follow it. Indeed, we found that if FDA's advice were followed nationwide one out of every four pregnancies would be exposed to a maternal blood mercury level above the NRC recommended level for at least one month. That is a quarter of all pregnancies.

Let me make clear our goals. We want the FDA to, one, adopt the NRC, NAS blood level for methylmercury. We

know that is beyond the charge of this committee today but we mention it because it is critical.

We want FDA to conduct a one-time sample of the top 40 or 50 most consumed fish, particularly those where they have very limited data, so that the agency is operating from a position of knowledge when advising pregnant women on fish consumption. This testing should include important seasonal sport fish that can be a significant source of mercury for thousands of pregnant women.

They should conduct and make public a state-of-the-art Monte Carlo style exposure and risk assessment of fetal mercury exposure. They should issue a mercury health advisory that protects 99 percent of the pregnant women at least for methylmercury while, at the same time, recommending fish and other foods that are low in mercury and high in omega-3's. This second step is critical because it is the list of safe fish that makes possible a truly comprehensive list of fish that pregnant women should avoid.

We are not asking for tolerance of methylmercury nor a lowering of the mercury action level. The action level is not enforceable; it is not enforced; and it would do as close to nothing to protect pregnant women and their

children from mercury as any action the government could take.

Above all, we are asking the FDA to change the way that it looks at fetal risks for methylmercury exposure. All the pregnancies at risk for methylmercury occur above the 98th percentile of exposure, as Jane will explain. But this is a huge number of pregnancies, as many as 400,000 per year. FDA has been overlooking these exposures and the seafood industry has been more than eager to support this policy.

This attitude and approach is no longer acceptable but, more importantly, it is no longer necessary. There are sufficient data on mercury levels in canned tuna, tuna steaks and several other fish to support their addition to the FDA methylmercury health advisory. For scores of other important fish, the FDA only needs better data on fish contamination with mercury to issue a sound advisory. The agency stopped monitoring seafood for mercury in 1999, as I presume you have heard, and we presume that everyone would agree that this program needs to be restarted and that the FDA needs to monitor the seafood supply for mercury.

With better data on mercury contamination of fish, the FDA could monitor mercury exposure for nearly all important fish with reasonable confidence at the 99th

percentile of exposure and above, enough confidence to support a strong protective mercury advisory for pregnant women and to produce a list of fish that are low in mercury and safe for consumption during pregnancy.

A protective mercury health advisory for pregnant women is not about banning tuna consumption, although we feel quite strongly that pregnant women should avoid canned tuna. And, it is not about denying women the benefits of omega-3 fatty acids. It is about developing a health-based standard for mercury exposure that protects all the nation's unborn children from unsafe levels of mercury, while providing nutritional, low mercury alternatives for these same women.

The seafood industry and their consultants would love this, an argument about the future of the fish industry and about how ill-informed consumer advocates want to deny women and children the proven health benefits of fish consumption. Nothing could be further from the truth. Women should eat more fish. There is no doubt about that. At the same time, women should be protected from mercury. There is no doubt about that. What the seafood industry would have you believe is that you can't have it both ways. You either have no fish or suck it up and eat the mercury. It is very effective PR and it is simply not true.

In the midst of this onslaught, the FDA rightly sees itself with two obligations, to protect the fetus from methylmercury exposure and to provide those developing babies with the best nutrition possible. The problem is that the agency has adopted essentially the industry view that these two goals are mutually exclusive. Until today or this meeting, the agency had essentially given up trying to protect women from mercury in seafood. They stopped monitoring seafood for mercury in 1998. They have not adopted the NRC recommendations for mercury levels in blood, and they have not provided a sound rationale for not doing so, and they have not been able to provide the Congress, or anyone, with a physical, actual copy of a risk assessment underlying their health advisory.

In the end, the agency limited its methylmercury health advisory to a short list of fish based on antiquated science and a misplaced fear that a longer list would deprive women of the nutritional benefits of fish. Yet, at the same time, the agency has done nothing to help women identify the fish and other foods that are low in mercury and high in omega-3 fatty acids. This is particularly ironic because it is precisely the creation of a good fish list that would provide the nutritional rationale for a comprehensive list of fish to avoid during pregnancy.

When Jane and I met with Joe Levitt and his staff, he asked us what we wanted and I will tell you today what I told him then. Don't laugh--we want a refrigerator magnet or a card a woman can put in her wallet with two lists of fish on it, one, a list of mercury-contaminated fish that women should avoid when pregnant and, two, a list of fish that are low in mercury and high in omega-3's that pregnant women should eat more of. Very simple. This is not a complicated problem.

We then want the FDA to work with healthcare providers, not the seafood industry, to ensure that every pregnant woman in America gets these simple lists, just like lead. No regulations. No tolerances. No bans on any fish. Just the best information based on the best science available on how pregnant women can protect their babies from mercury and provide them with good nutrition at the same time. Thank you.

MS. HOULIHAN: I have some copies of the presentation I am about to give. Good afternoon. As Richard mentioned, I want to share with you, maybe not so briefly, some of the analyses that we have done regarding methylmercury exposures in women of childbearing age. I understand you had some presentations made yesterday that also looked at this issue so some of this should sound a little bit familiar.

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First of all, I want to talk briefly about what led us to do this work.

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As you have all heard by now, on January 12, 2001 FDA issued its first consumer advisory to pregnant women regarding methylmercury in seafood. That advisory contained two main points. First of all, pregnant women should completely avoid eating four fish, shark, swordfish, king mackerel and tile fish. The second part of that recommendation is that pregnant women can safely eat up to 12 oz of any other kind of fish throughout pregnancy.

We have done work on methylmercury in the past and we are familiar enough with the mercury data to know that there are some fairly high mercury fish that did not appear in FDA's advisory.

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So, we asked ourselves the question at that time what would happen if a pregnant woman followed FDA's advice and actually did eat 12 oz, or about two servings of fish a week, except for shark, swordfish, king mackerel and tile fish. The pertinent question is would her mercury exposures exceed the safe levels that have been derived from available epidemiology studies, levels recommended by

the National Academy of Sciences and applied by the Environmental Protection Agency for example.

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I am going to jump straight to the answer to that question before I give more details of the model. The answer is, and I will explain the graph in a second, that the model shows that if pregnant women followed FDA's advice and ate 12 oz of supposedly safe fish a week, and ate that in normal national consumption patterns so they are far more likely to eat canned tuna, for instance, than any other kind of fish, more than a quarter of all pregnancies would be exposed to mercury at levels above the reference dose for at least a full month of pregnancy.

The graph is a little complicated but, of course, the X axis is total time during pregnancy. That is any three-month, any four-month, five-month chunk of time during pregnancy. On the Y axis we have the percent of babies exposed in utero to methylmercury levels above the reference dose for that given time span or longer.

For instance, if you look at one month on the X axis and go up through the graph, you are seeing about 28 percent of all pregnancies that would be exposed to methylmercury above the reference dose for at least one month of pregnancy. You also see maybe midway through pregnancy, say, four and a half months, that you are almost

at one in ten pregnancies being exposed above the reference dose for half their pregnancy if women actually ate 12 oz of fish and followed FDA's recommendation.

I will get into the details of that model and how we produced that answer, and also in this presentation I will focus in on some other examples.

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This is really the outline of my talk. First I will talk about our modeling method and go into more detail on the results and how those were produced. Second, I will describe some of the underlying biological parameters in the model. That would be things like how a woman absorbs and excretes mercury. Third, I will talk about fish consumption and now much fish do women really eat. Of course, there aren't a lot of women eating 12 oz of fish a week but I will look at proportions of women who do eat a lot of fish, based on national databases. Fourth, I will talk about methylmercury exposure, in particular focusing on canned tuna because it is the top seafood eaten in the U.S. and a lot of high seafood consumers focus pretty heavily on canned tuna. Fifth, I will highlight some other examples from real-world data user examples that are found in government and market company databases of real women reporting large amounts of fish that were actually eaten during different periods in their life. Last, I will just

sum up what we would like to see come out of FDA on the subject.

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Modeling approach, the underlying structural technique in this model is called a Monte Carlo method. It is a probability method. What it is really good at is allowing for an accounting of biologic variability. Differing individual consumption patterns and ranges of mercury concentrations in seafood are all incorporated into the model. So, compared to, say, looking at an average woman paired up with a high end consumption, this model lets you look at the full range of exposures across the population accounting for the fact that people are different; they eat in different ways; and they are eating seafood that varies widely in its concentrations of mercury.

Second, the underlying mathematical representation in this model, is a non-steady state or transient one-compartment pharmacokinetic model, developed and verified--one place it is presented is Dr. Gary Ginsberg's work from the Connecticut Department of Public Health in peer reviewed literature. It is a model that looks in particular at mercury concentrations in blood and how they vary with time as a woman eats seafood.

How do we vary the way that women eat seafood? We account for biologic variability in a couple of different ways. We rely on data from CDC's National Health and Nutrition Examination Survey, or NHANES, and we also rely on studies of absorption and excretion of methylmercury that appear in the peer reviewed literature, which were summarized in a paper written by Alan Stern, of the New Jersey Department of Environmental Protection, that appeared in peer reviewed literature in 1997.

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The model also accounts for the different ways that people eat seafood, different consumption rates. The scenario I showed you first, which is everybody is eating 12 oz of fish a week, is a hypothetical scenario. But today I will present data that is based on real consumption data from national databases that include low fish eaters and high fish eaters as well. We used two different databases to do this. One is CDC's newly released 30-day recall seafood consumption study that includes over 1000 women of childbearing age and what they ate in the past 30 days. We use that in combination with the National Eating Trends database from a major market survey organization, called the NPD Group. This database we use in particular because it is really powerful. It contains data on almost

8000 women so it is many, many more women than CDC's recall file.

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Lastly, mercury concentrations in seafood, the model accounts for the widely occurring concentrations of mercury in different fish species. To account for that, we compiled mercury data from seven different government databases of mercury and fish tissue. These came from FDA, NOAA and EPA, seven databases and 50,000 records altogether of numerous different fish species.

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I will just talk briefly about how a Monte Carlo model works, for those of you who haven't used this technique before. It is conceptually pretty simple. You know, you start off any model with the exercise of what questions you want answered. So, we are first of all answering the question what would happen to mercury exposures if pregnant women followed FDA's advice and ate 12 oz of fish a week throughout pregnancy, barring the four black-listed fish. Would her mercury exposure exceed safe levels derived from available epidemiology studies?

The first step in the model is that the model begins simulation. It basically creates a woman and the model randomly assigns that woman a unique combination of body weight, blood volume, the fraction of mercury that

will be absorbed through the gut and the fraction of that mercury that will be distributed to blood as opposed to what is stored in other tissues, like the brain, and an elimination rate constant which is a measure of how quickly a woman can excrete that mercury from her body. So, that is basically the model, a person in all her associated biologic parameters that all come from measured data in the peer reviewed literature.

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The second thing the model does, it assigns this woman an initial blood concentration. In other words, women are eating seafood throughout their life and at some point, you know, a woman who decides to have a child gets pregnant and she has a starting concentration of methylmercury in her blood. That is called her initial methylmercury concentration and that is where the model starts her off as she begins to eat seafood through pregnancy.

The third thing the model does is it allows the woman to eat the prescribed number of fish servings through pregnancy, so in this case, if I am doing two servings, two 6 oz servings of fish a week, it will loop her through two meals per week in the model.

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As it does that, it does the fourth thing, which is track the woman's blood mercury concentrations as she eats fish through pregnancy. The program maintains statistics on her blood mercury distribution through time. So, in other words, a woman eats the fish. A fraction of the mercury in that fish is absorbed through the gut and is distributed to the blood. Through the bloodstream, it is then distributed to the various tissues in the body and then is excreted through time, depending on that individual woman's excretion capacity.

This is where the Monte Carlo part comes in. It repeats that, in this case, 299,999 times for example. So, in essence, it simulates 300,000 unique women and at the end of the model we can compute composite blood mercury statistics on that whole population of modeled women.

So, you can see how this modeling technique is really powerful because you are essentially creating women in this model based on real biologic variability and some of them will be particularly sensitive to mercury, will absorb a higher quantity, excrete a lower capacity, and those women, in combination with high consumption rates, is where some of the biggest problems lie and the model takes all that into account.

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When we did this exercise of two servings of fish a week, as I have already discussed, this is one of the basic answers that came out of the model, that women really cannot safely eat two servings of fish a week through pregnancy and FDA's advice. If women actually followed it, you know, more than a quarter of all pregnant women would be in a zone that exceeds a safe level for at least a month of pregnancy.

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Another thing that this model lets us do is segregate fish according to their relative safety. For instance, I can construct fish scenarios where I say let's let a woman eat sea bass and nothing but sea bass and see what that does to the answers in the model, how women fare. It turns out that sea bass, tuna steaks, halibut and white croaker are high enough in mercury, according to the measured data, that if women routinely ate those fish, or ate almost any of them, they would put themselves into a zone where their mercury levels might exceed safe levels.

This chart is a little hard to read but it does segregate out by species which is one valuable thing we can see. On the X axis is how many meals per month of that particular fish a woman would be eating, so a meal per month up to two meals per month basically on the bottom of the chart. Then, the Y axis is the percent increase in the

number of women whose blood mercury level exceeds the reference dose for more than a month of pregnancy. So, this is fixed at one month.

But you can see that sea bass, tuna steaks, halibut and white croaker have really high mercury concentrations relative to the fish that fall out at the bottom of the chart. At the bottom of the chart we have things like salmon, wild Pacific salmon, farmed catfish, farmed trout, summer flounder. They are all much lower in methylmercury concentrations and, therefore, are associated with much lower risk levels as women eat them through pregnancy. So, the take-home message is that individual species vary pretty widely in their mercury concentrations.

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I want to briefly go over some of the underlying biologic parameters in this model. The biologic parameters that govern absorption and excretion of mercury, as I mentioned, were taken from the NHANES program and from combinations of studies that appear in the peer reviewed literature, largely summarized by Stern in a paper from 1997.

Body weight of women is assigned at the beginning of the model. We used data for 4935 women of childbearing age from CDC's NHANES survey.

Blood volume is calculated from body weight. Blood volume correlates really strongly with body weight and increases, of course, as body weight goes up.

Elimination rate constant is a measure of how quickly a woman can excrete mercury from the body. It follows a first order exponential decay pattern according to a number of studies in people, with a mean and standard deviation that I give here.

Fraction of ingested dose that is absorbed--every woman has her own unique capacity to absorb mercury through the gut after she eats the fish. The fraction of that absorbed dose is then distributed to the blood. So, the mercury enters the blood and is distributed throughout the body, goes to various tissues where it is stored, brain and other tissues, but some of it remains in the blood and that is the concentration that we keep in the model.

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This is just what the initial concentration distribution looks like. This is data from NHANES arbitrarily separated out by age of women so you can actually see all the dots. But there are 1645 women whose blood mercury was measured in CDC's latest NHANES data release. One reason I post this is because it has become pretty apparent from work, in particular by Ben Raines, in Alabama, that when you focus studies on women who are

frequent fish consumers, these women aren't necessarily represented in this data set. Ben Raines tested mercury in 65 women and he found that 51 of those women exceeded the reference dose in his measurements. So, some of them are a substantial amount higher than what is shown in this population of 1645 women.

What we do know is that in that data set, although it is a large data set from CDC, we are not necessarily representing women who eat a lot of fish. There are a lot of women missing from that.

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Fish consumption--I just want to talk a little bit about the fish that women eat. As I mentioned, we rely on two primary databases to look at consumption. One is the 30-day seafood consumption recall file from CDC's NHANES program released a couple of weeks ago. The other is the National Eating trends database that gives us data on approximately 8000 women. I focus on that database here because it gives us so much more resolution at the tail where women are really eating a lot of fish.

When we break that data down we find a lot of women in that tail and this is, in particular, focused on canned tuna. So, this graph basically highlights how many women are eating a lot of canned tuna. Let's just look at that center bar which is five or more servings of tuna per

week. This is women who eat five or more canned tuna servings per week. When we extrapolate the data out to the population of women of childbearing age that corresponds to 52,000 women. There are also women who even eat seven servings or more of tuna a week. Three or more servings of tuna, 210,000 women of childbearing age, when you extrapolate this data, they are eating at least three servings of tuna a week. If we focus on the 52,000 women that are eating five or more servings of tuna a week, I can safely say that all those women will be above the reference dose for methylmercury.

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So, I did a simulation looking at real consumption patterns pared down to only canned tuna so this is nothing except canned tuna. This is measured data from 8000 women. They are true consumption patterns, extrapolated to represent all women of childbearing age.

I want to talk for a minute about concentrations of mercury in canned tuna because that, of course, is an integral part of this model and the scenarios that I do focus on are canned tuna. In our database we have 479 test results for canned tuna. Most of these come from FDA. FDA tested 219 samples in a special canned tuna survey in 1993. We have 115 samples from FDA's seafood surveillance database before they stopped testing domestic seafood; 27

samples from the total diet study and we have supplemented that with relatively new data from the State of Florida with 118 samples that they submitted to FDA about the time that the advisory was issued.

So, we have a lot of canned tuna data. You can see that it varies widely in concentration, averaging about 0.2 but there are many individual cans of tuna that have concentrations far above that. I understand Dr. Aposhian tested cans of tuna and had a result even exceeding what is on this chart. So, there are a lot of cans of tuna that have very high levels.

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I ran the model using real consumption patterns for women of childbearing age. As it turns out, the consumption comes from 7319 women of childbearing age who eat canned tuna. We find that even forgetting all other fish, canned tuna consumption alone drives high blood mercury because it is such a high proportion of seafood that is eaten in the United States. There are about 40,000 pregnant women every year, and this is based on real consumption data so this is a picture of what is actually happening, an estimation of what is happening. There are 40,000 women in the U.S. every year, pregnant women who exceed the reference dose for at least three months of pregnancy based on canned tuna consumption alone. That is

the bar that is associated with three months. So, they are over the safe dose for at least three months of pregnancy. That is 40,000 pregnancies. That is one percent of all pregnancies in the U.S. just from canned tuna.

If we think about women exceeding the safe dose for at least a month of pregnancy, we are up to about 90,000 pregnancies going over a safe dose just from canned tuna consumption. So, you can see that the canned tuna consumption really drives a good percent of the risk in the U.S. in terms of women who are facing high methylmercury exposures.

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I next focus in on a particular woman in a model, just a little window of what is happening in the model to the mercury in her blood. Between days 12 and 22 of the model she had a number of eating occasions in which she ate canned tuna that had quite a bit of mercury in it. You can see that her intake is exceeding her excretion capacity. That is what happens in this model, blood levels can build up and then decline. If you exceed excretion capacity, your mercury levels go higher and higher, and then maybe you eat some more mercury fish and levels decline but the model is accounting for all of that. So, you can see her mercury level is building up through this ten-day period just because of the tuna fish that she is eating. She is a

frequent tuna consumer. She is eating it almost every day but the same thing happens for women who are eating it less frequently.

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The next thing I did was a basic reality check on the model to see if it was consistent with what CDC had measured. The top blue line is the real world. That is the distribution of blood mercury levels that CDC measured in women of childbearing age, and it represents--what?--11600 women. That is the real world. Blood methylmercury concentration is on the X axis. The Y axis represents the percent of women who are at or below that methylmercury level. For instance, about 20 percent of all women are at or below 2 ppb of methylmercury in blood. That is how you would read that.

Now, if I plot on top of that one of the answers from our model, the red line, that red line is the model results. It is a snapshot of blood mercury levels at model day 100. I could pick any day of the model. This happens to be model day 100. That is the distribution in all 300,00 women in the model at model day 100, what their blood mercury distributions looked like.

As you would expect, you can see, number one, canned tuna consumption doesn't account for all the methylmercury in the population but it accounts for a

substantial fraction. It is consistent with consumption patterns in the U.S.

The second thing you can see, and this is important, if you subtract one line from another, so if you take background exposures that are represented by CDC's data in that top line and you subtract out the canned tuna line and you are basically saying let's look at what happens if people don't eat canned tuna, you suddenly find the exposures are substantially lower and you are getting a much higher percentage of women who are in a safe zone throughout pregnancy. So, the bottom line is canned tuna is a big driver of women exceeding a safe dose during pregnancy just because consumption is so very high, especially at the tail end of the data.

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That is canned tuna. That is real good consumption data. I want to point out a couple of other examples of particular women where we know their consumption pattern in detail. First of all, FDA conducted some focus groups in the fall of 2001 which are real interesting reading if you are so inclined, but there are a number of women in these focus groups who talked about how much fish they were eating or did eat during pregnancy.

One woman said in these focus groups, "when I had my first son I had gestational diabetes and I was put on a

very strict diet, and one of the things I could eat was a can of tuna and two tablespoonfuls of mayonnaise for lunch every day, five days a week." She said, "so every day, five days a week for lunch, for seven weeks of my pregnancy, so for seven weeks I am eating more than they recommend." So, she ate tuna every day for seven weeks, and that is perfectly consistent with some of the data that is in the measured databases.

A second woman said, "I was doing it, eating canned tuna, because I was planning to get pregnant and as part of the Atkins diet you can have stuff like that, fish or chicken. So, I ate a bag of salad, a can of tuna. That was my lunch." So, she was on a special high protein diet and she was eating a lot of canned tuna.

Let's look at what the databases tell us about how consistent those anecdotes are with real-world data. Well, in CDC's NHANES 30-day recall seafood consumption database, there is a 29-year old woman who reported eating 30 servings of tuna over 30 days. She eats canned tuna every single day. In the National Eating Trends database two women, ages 22 and 24, reported eating 15 servings of canned tuna over 14 days, about a can a day. A 23-year old woman reported eating 14 servings of canned tuna over 14 days. So, there are people for whom canned tuna is a staple. They are eating it every day for lunch or dinner.

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I took one of these examples and ran it through the model. I looked at the focus group woman from Calverton, Maryland who said she ate a can of tuna every day for seven weeks of pregnancy. She delivered early so that was the end of her pregnancy, but during that seven-week time, if you think of the Y axis as the percent chance that she would go over a safe dose for this given time span during her pregnancy, let's look at four weeks. For that seven weeks of pregnancy there is about a 65, 70 percent chance that she will go over the safe dose for well over half of the rest of the duration of her pregnancy. So, she has substantial chances that she is over the safe dose through almost all of the remaining period of her pregnancy. That is just seven weeks. So, for women who really are eating a lot of tuna throughout their entire pregnancy, they are getting into very high probability that they are exceeding the reference dose through almost all of their pregnancy.

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The next thing I would point out is that this is women who happened to eat fish that Ben Raines tested from the Gulf of Mexico. He tested a handful of fish. One was an amber jack that was caught in the Gulf of Mexico and had a mercury concentration of 1 ppm. The other was a yellow

fin tuna that had a concentration of 0.83 ppm of methylmercury. These are averages based on number of samples. If a woman ate that fish for four servings of that fish at the beginning of her pregnancy so she is only eating four servings of fish only over four days--the time span during pregnancy is shown on the X axis and the percent chance that she would be exposed to methylmercury reference dose for that time span or longer is on the Y axis. So, if we just look at, say, one month she is going over the reference dose for at least a month of pregnancy.

We see for the yellow fin tuna there is a 60 percent chance she would be over the reference dose for at least a month. For the amber jack, she would be up to an 80 percent chance that she would be over the reference dose for a full month of pregnancy.

So, you can see these fish with high concentrations which are in the database--these fish are out there, they are being sold in the marketplace, and a very few servings of those fish will really drive a substantial percent chance that a woman would go over a safe limit for a long period of her pregnancy.

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Last, our recommendations to FDA--because FDA has really such a limited consumer advisory to pregnant women, a lot of states are taking up the slack and trying to give

women supplemental advice. There are at least nine states that advise women to limit their tuna consumption, and I think Michael Bender will talk about this in more detail later. Connecticut, for instance, you know, fresh tuna once per month, canned tuna one to two meals a week; Wisconsin, one meal per week of canned tuna, one meal per month of fresh tuna; Michigan, one meal per week of canned tuna.

You know, FDA is advising women that they can safely eat up to 12 oz of fish a week that includes canned tuna and tuna steaks, and these states have said, wait a minute, that might not be safe. So, they have tried to issue some supplemental advice to women to get the message out about mercury in fish that FDA does not have in their advisory.

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This is a plot of omega-3 fatty acid content, a rough estimate of omega-3's in various kinds of fish versus the mercury concentrations in those fish. The wide bars are the omega-3 fatty acid content. The first point is that fish vary pretty widely in their omega-3 content. This is an average level based on USDA's nutrient database for that group of fish that I show on the X axis. Herring, sable fish, salmon, very high in omega-3's. Scallop and

clams are on the other end of the graph, generally a lot lower in omega-3's, and everything else is in between.

On top of that you see the dark bars. That is average methylmercury concentration in those fish. It is interesting to note that there doesn't seem to be much correlation at all between omega-3 content and methylmercury concentration. The good news in that is that they are not mutually exclusive and it is possible to come up with a list of high omega-3 fish that are low in methylmercury. One really great example of that is wild Pacific salmon, which is the third fish over on the bottom. It is very high, on average, in omega-3 fatty acids and very, very low in methylmercury. So, that would be a great fish according to the data that we have in-house for pregnant women to eat during pregnancy. They could safely eat it and still get the nutrients that they need.

Let's also juxtapose a couple of examples of how many of these fish FDA has tested. For herring, which has fabulously high omega-3's on average, FDA has eight samples. Whitefish, high in omega-3's and you would want to be able to recommend that to pregnant women and FDA has tested two whitefish. They have tested two bluefish; about ten of some of the species of sea bass, ten snapper, ten perch. So, methylmercury sampling has not been sufficient, to say the least.

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FDA's summary, their own summary that is on their web site--they released a summary of methylmercury concentrations in seafood after they released their consumer advisory, and it shows that their monitoring program has major testing gaps. They focused their testing really heavily on seafood that women are advised not to eat. For swordfish, for example, they have 598 samples listed; for shark, 394 samples. I pointed out some of the other fish that have promising sources of omega-3's for women, and there are only two tests for whitefish, two for bluefish, eight for herring, ten for ocean perch, nine for orange ruffy. In so many cases the mercury concentrations have not been adequately characterized that you could actually be certain that women are getting good advice if you recommended those fish for them to eat during pregnancy.

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The bottom line, I just want to reiterate some of the things that Richard said. This is what we would like to see FDA do. We would like for FDA to adopt the NAS recommendations for a safe level of exposure.

We would like FDA to conduct a one-time sampling program for the most consumed fish species. For so many of these fish there is not enough data to fully characterize

mercury concentrations. We want FDA to do a major one-time sampling program of, say, the top 50 fish eaten in the U.S. to really get a grip on what is going on with the mercury.

Third, we would like FDA to conduct and make public a risk assessment, to do a risk assessment. We are recommending a probabilistic exposure risk assessment that would allow FDA to get really good resolution at the tail end of the data where women are consuming a lot of fish.

Number four, we would also like FDA to issue a public health advisory that protects a very high percentage of women from mercury exposure that exceeds the NAS recommendations and that ensures women eat low mercury fish, high omega-3's. As we saw in the canned tuna data, about one percent of women are going over a safe dose under model predictions for at least three months of pregnancy just from canned tuna consumption, and that really is what is happening based on all the data that we have put together. Those exposures could be mitigated if FDA would give the public, particularly women, comprehensive advice on what fish to avoid during pregnancy and what fish they should eat during pregnancy that are high in omega-3's and low in mercury.

That is all I have to say. So, is it question time?

Questions of Clarification

DR. MILLER: Thank you. Comments? Dr. Nordgren?

DR. NORDGREN: I have two questions. The first is how accurate do people estimate these 30-day recall things are for actual fish consumption? The second question is, is there any evidence out there--if fish are like humans, there must be tremendous levels in variation in species so if you measure a shark in Cape Cod versus somewhere else, why aren't their levels fluctuating, and why only one sampling?

MS. HOULIHAN: Why not more sampling? So, the first question was how accurate is the 30-day recall file. That is a question I don't have an exact answer to, but I can tell you that it is the most comprehensive long-term survey done by the government on safe food consumption. That is not the underlying data in the scenarios I presented today. I used the National Eating Trends database, which records what you eat as you eat it for 8000 women. It is a food diary that is kept for a two-week period. It gave me so much better resolution at the tail end of the data that I used this for the canned tuna scenarios. I think the 30-day recall file is generally consistent with the NPD data though there is a substantial fraction of women in that who are eating a lot of seafood, reporting eating a lot of seafood.

The second question was why not test more. We are sort of calling on FDA to do a big one-time sampling program because we think that would be a fabulous start. And, that is the kind of underlying data that you would want FDA to have as they go through doing their own risk assessment and exposure analysis. There are many species of fish that I was not able to include in my model because there is just not enough data. So, for FDA really to take a good initial comprehensive look at this, they need to do a comprehensive sampling program. I would advocate for continuing to test for mercury, but I think a big one-time testing program of a lot of samples for the top fish is a really good place to start.

DR. MILLER: Johanna?

DR. DWYER: Do you mean actually do the mercury analyses in these various types of fish, or do you mean collect data that already exist in the literature and put them into some uniform database? Which is it? Are you calling for the analytical work, or informatics work, or both?

MS. HOULIHAN: Both would be fabulous because there are a number of states who have tested some marine species that maybe FDA doesn't have data for. But, you know, FDA should conduct their own comprehensive sampling program at the same time. It makes a lot of sense for FDA

to try to get together a comprehensive database of what has been done to date as well for methylmercury testing in seafood.

DR. MILLER: Dr. Russell?

DR. RUSSELL: Thanks for the very clear analysis that you have given. Your analysis, of course, is based on the acceptance of the NAS guidelines, which was based primarily on the Faroe Islands study. The other serious scientific attempt, it seems to me, to arrive at a safe level was the ATSDR study or analysis using as the lead study the Seychelles study, which came out with a level that was 0.3 instead of 0.1 as being a safe level. Can you explain how you analyzed or what you thought of that ATSDR analysis and why you rejected it, or why it is being rejected in favor of the NAS study? Is it because it is more conservative and you want to err on the safe side, or are there some other reasons, scientific reasons?

MS. HOULIHAN: You know, in the world of risk assessment or toxicity risk assessment in particular, it is pretty traditional when you are trying to protect public health to look at the study that showed measurable effects at the lowest levels and to use that as a basis for public health protection. I think that makes a lot of sense. Instead of choosing a study that showed a higher level, you

want to do something that actually ensures a higher level of protection.

No one is disputing, I think, that they are credible studies, the Seychelles, Faroe and all the other studies that have been conducted, but the idea behind risk assessment is to take the data as a whole, look at the most sensitive endpoint and apply that as the starting point for your reference dose.

DR. RUSSELL: Just to carry that one step further, I agree in general. Another question that I would have for you is do you think that the Faroe Island study is more comparable to what happens in the U.S., or do you think the Seychelles study, with regard to dietary patterns, is more comparable?

MS. HOULIHAN: I think there are a lot of women in the U.S. who eat a lot of seafood. I will say that. I know that there were questions brought up during the National Academy study of possible confounding with PCBs, and those questions were addressed. It is not PCBs, it is methylmercury that seems to be associated with the neurodevelopmental decrements. There are other studies as well that show consumption patterns that closely resemble ours where we don't have those sort of episodic spikes where effects are seen in those consumption patterns as well.

I would also say that when we are modeling methylmercury in blood we are not really reproducing the spikes. In the model results that I showed, when you see a spike in the model, that is not the true spike. I did neglect to point that out, that that is already the post-distributed mercury concentration.

DR. MILLER: Dr. Lee?

DR. LEE: Somewhat as a follow-up, I admire your conservative approach, erring on the safety of the women and the children, but both the Faroe and the Seychelles studies were done in a double-blind fashion so you remove any investigator bias. But it seems to me that in this modeling study that you did you selected data based on a conservative outcome that you knew. So, some of the model variables that you have picked, like the body weight and the blood volume and elimination, could have been influenced by the need to demonstrate the outcome.

MS. HOULIHAN: You are saying that I chose biologic parameters that would drive up mercury exposures?

DR. LEE: No, I am saying that you didn't choose your parameters in a double-blind or even in a single-blind fashion. You were looking at data that would help demonstrate the need for action.

MS. HOULIHAN: I chose the underlying biologic parameters that are in the model based on what is in the

peer reviewed literature and I didn't cut anything out. Say, for instance, elimination rate constants and the volume that is absorbed through the gut, those were taken from a survey that Dr. Stern, from New Jersey, did where he considered all the available data from the peer reviewed literature and I don't think he purposely cut any data out of his analysis.

DR. LEE: Okay, that was a review that Dr. Stern did?

MS. HOULIHAN: Right, a paper he published in 1997.

DR. LEE: So, is that all the available information on that absorption?

MS. HOULIHAN: Well, that is an issue that FDA should take up as they build their own model because there have been data published subsequent to Dr. Stern's review that should also be included in those kinds of distributions. That is an important question.

DR. LEE: Okay, thanks.

DR. MILLER: Dr. Fischer?

DR. FISCHER: I would I guess have a comment that your whole presentation seemed to indicate, at least to me, that you knew what level of mercury exposure was safe and what level was unsafe and that, of course, was the EPA RfD. Except, I think we all, from our discussions up to this

point, have heard other people say that they weren't certain exactly what level is safe and what level is unsafe.

The fact is that we really don't know where the safe level is at this point. What we have to work with is a number that comes from a risk assessment procedure which can be used for regulation. So, the terminology that is used, safe versus unsafe, when used in the way you are using it tells the public that they are being subjected to a lot of risk that they believe is actual. But we know there is a lot of uncertainty.

I just wish, for example, when you presented your data from your model that you would have shown us, instead of percent of women above a certain regulatory level, the model blood levels of methylmercury of these women, or hair levels so we could compare with actual blood and hair levels that have been seen, like the NHANES levels and others. It would allow at least me, who looks at blood levels and hair levels, a better picture of actually how well your model is doing.

MS. HOULIHAN: Well, you will see in your slides that I did present a picture of the blood levels, the composite model results from all 300,000 women and compared them directly with CDC's background distribution. So, you can look through your presentation slides and see exactly

the distribution that the model predicted from real consumption patterns.

I agree there will always be uncertainty in these kinds of problems for what level is toxic to a particular person, what is safe, what is not safe, is there a safe level of exposure but in the end, when you are doing a risk assessment and trying to protect public health you have to make decisions. For instance, what percentage of the population are you trying to protect from what level of exposure, and you have to make those decisions in order to do the risk assessment and protect public health. Whether that is a bright line, a fuzzy line, a grey line, you know, I don't know but right now there is not really a line; it is just don't eat sharks or king mackerel or tile fish, and that is not really doing it for keeping blood levels down to levels that the National Academy and the Environmental Protection Agency say are protective of public health.

DR. FISCHER: I understand perfectly the decision-making process. It is communication that I am talking about. Whether it is scientific or not scientific, it seems to me we should be honest and truthful about how we are presenting the information to each other and to the public. It is a matter of semantics I guess.

MR. WILES: We would be glad to provide the committee with blood level distributions for any particular

slide that was up here, if that is going to help clarify matters in any way.

DR. FISCHER: Yes, I would like to see the blood levels. Wonderful.

MS. HOULIHAN: Yes, if you have a particular thing you want to see besides what I showed here, which is blood levels for a particular period of time, I could show you other periods of time or other scenarios if that is interesting or useful.

DR. MILLER: Dr. McBride?

DR. MCBRIDE: I may be confused a little bit by your model, but I understood you to say that you took into account the initial methylmercury levels in these women based on, I presume, a population study.

MS. HOULIHAN: Right.

DR. MCBRIDE: And then you added to that what would happen if they ate the top limit of fish.

MS. HOULIHAN: Right.

DR. MCBRIDE: Well, that doesn't take into account that a good number of them are already eating that or more.

MS. HOULIHAN: Well, on any day in the U.S. there is a particular distribution of blood mercury levels that is going on in the United States. So, the point when a woman starts pregnancy falls somewhere in that

distribution. She starts her pregnancy with one of those concentrations, and that is what the model does. It assigns her one of those concentrations. Then, through pregnancy she continues to eat fish. So, she is doing her thing, eating fish as she normally would, and days subsequent in her pregnancy she still falls some place in the U.S. distribution.

So, there is no inconsistency between using a measured set of population values as she begins pregnancy with then continuing to let her eat fish through pregnancy because that is what people do. What is important is that as the model runs and reproduces population-wide statistics, those statistics remain consistent with what we know about population-wide blood mercury levels, and that does happen when we check the model out. It is consistent with what CDC measures in the general population.

DR. MCBRIDE: Then, do I misunderstand to think that during your modeling the levels would all have to be higher?

MS. HOULIHAN: No, they do not. Some women drop off because they are eating low mercury fish or few fish.

DR. MCBRIDE: Women's blood volume goes up considerably in pregnancy, actually by a greater percent than their weight. Is that included in your model?

MS. HOULIHAN: That is not included and I haven't seen it in any assessments that have been done to date. The EPA doesn't consider it. I would have liked to add that to my model but I had trouble finding studies that would let me quantify that.

DR. MILLER: Other comments or questions? Yes?

DR. ACHOLONU: During your presentation you talked about the frequency in the consumption of tuna fish for instance. You say that eating it very frequently, you used the word, "drives up" the concentration of blood mercury. You also talked about the absorption and excretion of mercury. There are some studies that say that the half-life of mercury in the human blood is 70 days.

MS. HOULIHAN: Yes.

DR. ACHOLONU: And that you get a steady state or equilibrium between absorption and excretion in about a year if you are exposed to it every day. How does this ameliorate your fear about the frequency of eating tuna fish?

MS. HOULIHAN: Well, it doesn't ameliorate my fear at all for women who eat tuna really frequently. If they do eat fish frequently enough to reach what you would call in the modeling world a steady state, it is still a level that is much higher than the NAS and EPA recommendations.

DR. MILLER: Dr. McBride?

DR. MCBRIDE: How many ounces of tuna fish are in a typical small can of tuna?

MS. HOULIHAN: That is a 6 oz can or 3 oz small can.

DR. MCBRIDE: Three? So, the women eating two cans a week were eating 6 oz of tuna.

MS. HOULIHAN: Right, and in this model run that I showed that focused on canned tuna, it tends to damp out the tails. It doesn't show as many women in the high ends of risk because I fixed the model on a typical tuna serving. The next step if I continued this work would be to use actual measured distribution that includes women eating lots and lots of tuna as well as small amounts of tuna.

DR. MILLER: Dr. Shannon?

DR. SHANNON: If you could help me understand one issue that has come up repeatedly over yesterday and today, and that is establishing what mercury level in a woman would lead to unsafe concentrations in the fetus. I think we have been looking primarily at a blood level of 5.8 ug/L in a woman, assuming that that would correspond to a cord blood mercury of 5.8 ug/L. If the concentration of mercury in a fetus is 50 percent higher than the blood mercury in a woman, and I have heard many others say it is credible that

the cord blood level would be higher, then I guess I already know the answer but that would mean that you really should be looking at a lower blood mercury in a woman that is potentially hazardous. So, my question to you is have you looked at your model at that lower level of blood mercury in order to kind of explore what that means in terms of impact?

MS. HOULIHAN: No, but that is a great idea. I mean, it would obviously--well, I don't want to say it would drive the numbers up. Yes, it would make the risks higher.

DR. MILLER: Dr. Nordgren?

DR. NORDGREN: Would it be appropriate to ask Dr. Lockwood a question at this point?

DR. MILLER: It would.

DR. NORDGREN: Dr. Lockwood, a very simple question, are there good studies studying levels of methylmercury that you are aware of in pregnant women that changes? Are there any good studies that document what happens to methylmercury levels during pregnancy?

DR. MILLER: Dr. Lockwood, could you use one of the microphones, please?

DR. LOCKWOOD: It is a great question. In fact, I was thinking two things from a basic toxicology perspective. The first is from the fetus' perspective,

does a given level of mercury have the same effect at given gestational ages? You would assume that a first trimester exposure would potentially have a more toxic effect than an exposure later in gestation. We don't have the data to model that. I don't think they exist anywhere but if anyone has it, I would be interested in knowing that.

The second is that, as with many drugs and many substances, the volume of distribution of the drug in a woman's body changes across gestation. Metabolism in the liver, not that that is necessarily relevant to this particular exposure, changes and the entire metabolism of a woman changes, and it may alter either favorably or unfavorably the build-up of mercury.

So, it is a great question and it is another reason for the NICHD to have an RFA to address all these issues. But the answer from a theoretical perspective is, yes, it probably does. I don't know. I don't know the answer but it probably does.

DR. NORDGREN: But you are not aware of a study that has documented that?

DR. LOCKWOOD: No.

DR. MILLER: Any other comments? Go ahead.

MR. WILES: I just want to say one thing. These are all great questions and I just want to remind the committee that we are not expecting anyone to just adopt

this model. What we want is for FDA to go and do this on their own and, through an open and transparent process, address these questions. But let's do it. Let's use our model, the seafood industry model or whatever. We need to move forward with a real exposure assessment that gets at these questions because it is clear that something is going on at the high end of the curve here, and whether it is 40,000, 100,000 or 60,000, whatever the number is, we think it is clearly greater than zero and it needs to be addressed, and we think this is the general way that it needs to be done.

What we are basically saying is that the FDA needs to go ahead and do it, not necessarily per se our results, our model or the seafood industry model or whatever. So, I just wanted to clarify that.

DR. MILLER: Just as a matter of scientific interest, and you can't stop scientists from being scientists, when you looked at your model there is a difference in the increase in risk depending on how far above the RfD the blood concentrations are or exposure.

MS. HOULIHAN: In these simulations I didn't pull out results for particularly high values so it didn't distinguish.

DR. MILLER: But can your particular model give you a distribution?

MS. HOULIHAN: Absolutely, yes, to get statistics on even higher levels of exposure.

DR. MILLER: Or even lower levels.

MS. HOULIHAN: Or lower levels.

DR. MILLER: How many of those over the RfD are within ten percent of the RfD?

MS. HOULIHAN: Right, that can all be done if you guys would find that useful.

DR. MILLER: Thank you. If there are no other questions, thank you very much. Our next speaker is the long awaited Dr. Henry Anderson.

Wisconsin Advisory

DR. ANDERSON: I am a fairly late edition to the agenda here and I didn't really have the charge questions that you had or a clear idea of what you wanted to hear so I am going to give you a smattering of a little bit of everything as it relates specifically to Wisconsin.

[Slide]

I will begin with a little bit of our history as it relates to mercury; how our advisories for sport fish have gone over time; and then give you some of the information from what we consider to be a comprehensive type of program, not just development or issuing of advice.

[Slide]

Just to give you a sense of Wisconsin, while we are not the size of Alaska, we do have 40,000 miles of rivers and 15,000 lakes, all of which are teeming with fish, filled with tourists who want to harvest those fish.

[Slide]

We, of course, have a history of point source pollution. We are also part of the industrial Midwest. This happens to be the Fox River with one of the largest PCB sources at the time, in 1973. We also have mercury point sources as well. I am going to talk not about point source issues, but you have to keep in mind that when we deal with localized fish, if they are not pelagic species that move around a lot you have to pay attention to where the fish came from, the question of the sharks, or whatever. If you have a ground fish which lives in a given area and that happens to be where toxic waste has been dumped for a long period of time, those fish will be different than other fish.

[Slide]

From a public health perspective, over the years we have always advised that fish is good to eat. You may recall people saying fish is "brain food." It is also good for the heart and, kind of the Hobson's choice, it comes with toxic chemicals, as was mentioned earlier. Hobson's choice, if you remember your literature, was a buggy renter

in England who said when you want a horse for your buggy, you can either have the horse nearest the door or no horse at all. So, basically it is not a choice. You take the horse. It was always kind of thought, well, the choice is you eat fish and you take the mercury or you don't eat fish. In reality, the message we have been trying to give is that that is not true.

[Slide]

This is back in 1970 is when the mercury was first begun to be identified in the Midwest. This is from the Wisconsin Conservation Bulletin.

[Slide]

Here, in 1971, is one of the early publications pointing out where sampling of fish was going on and warning areas. This was the scientists issuing advice or fish consumption warning concerns.

[Slide]

It wasn't until 1975 that Wisconsin issued their first advisory. What was done in the early years was to use the FDA market fish as a reference.

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Basically, our target audience from 1975-86 was to provide the angler a qualitative comparison to market fish. People wanted to know how does this compare to the fish I can buy in the store. So, we were able to say,

well, this fish is better than the guidelines by FDA and in Wisconsin we were not giving advice on how much is safe, or how much fish can I eat. We were not risk based; it was strictly comparative--if you eat this fish you get four times as much as this basically, not commenting on the extent of the hazard.

Key messages, again, were to eat fish, avoid the most highly contaminated fish, target where you fished and the species, and then kind of common sense, easily remembered, small fish, younger fish, lower on the food chain are likely to have the least contaminants. Oh, people would always point out, "but where that battery manufacturer discharged, those fish we can wring the mercury out of." So, there are always localized sites and there will always be a need for specialized advice in local areas but, in general, common sense, good advice that people can remember is this type of advice and most states have been issuing this for many years.

[Slide]

Back in about 1986--I didn't go through all my old files because I couldn't get them back from the historical society in time, but early on what changed many of the states was FDA acknowledging that tolerance levels may not be appropriate for consumers who regularly eat locally caught fish; also the issue of cost benefit coming

into it, and so states were left with, well, we need to do something on our own and. At that time, being the last in the Great Lake States, Wisconsin decided what people really want and what we are being asked for is not which are the worst fish but how much can I eat. So, we got into the risk assessment business of trying to issue advice on how much fish people could eat. Again, the issue of safety is always a hot item. We tried to avoid the issue of safety.

[Slide]

So, what we came up with at the time was working with our border states. One of the common things you will find in issuing advisories is if you have a cacophony of voices, as we do at the national level which is partly why you are here, the public tends to say, "well, they can't agree, why should I pay any attention to this advice at all?" So, one of the things that we have done--there are portions of the Great Lakes where, if you are on one side of the boat you are in Michigan, if you are on the other side of the boat you are in Illinois, and the other Wisconsin, and if we all have different advice, it is the same fish and you just fish on the side that has the advice you want to follow. Obviously, that is not at all an appropriate thing but it was pointed out to us why don't you have the same advice on mercury? We share considerable

water with Minnesota so a lot of these advisories were done to have some uniformity at least on border waters.

This is just early on when we went to the assessment, we separated the advice for pregnant women and children, but predominantly pregnant women, from the rest of the population. This just goes through the advisory as it was done earlier. By the year 2000, we had 1200 water segments that we had tested, and for 340 of those we had some type of mercury advisory on.

[Slide]

Then, along came the EPA reference dose and we began looking at how would that fit with our current process and this just gives you what we came up with. We also felt, again talking with many of the other states, that it did make some sense. There was the strongest evidence for a sensitive population. You notice we aren't saying women and children because there may be more sensitive populations than just them. Those are the ones the scientists have focused on.

The general population is another group, again recognizing that the reference dose is supposed to accommodate all individuals, and much of the uncertainty was related to adult effects from the different studies. Two of them showed cardiovascular effects at levels actually lower than for the growth and development issues

for the fetus, and 0.05 fit with our previous advice of where we would put an unlimited consumption level, from there up to 0.22 is about the one meal per week level. Then up to 1. We really didn't want to be issuing advice or recommending eating fish that were over the FDA tolerance so we have sort of drawn the line at 1, as you can see, in the general population. You can do with one meal a month up to 2.81 ppm in the fish tissue. We felt that we would rather keep it at a lower level and be consistent at least on the end with the common sense of, "well, if it is safe to buy it in the store it ought to be safe for me to eat." Conversely, "if I can't buy it in the store there must be something wrong with it." Therefore, it was fairly well accepted to keep the 2 on the top end but issue advice separately below that point.

[Slide]

When you look at that slide and you look at our fish tissue samples, basically we have very few fish that are below 0.05. So, going to multiple advice levels we really felt we needed to take a look at a more general guideline. We were also hearing from the public and some of our survey work that, in fact, we had gotten a very small segment of the population. When they catch a fish, do they note the time of the moon, the size of the fish, where they caught it, time of day, look what was in its

stomach? They have a log going back over all the years. Those people who are very data oriented, they wanted to know exactly how many inches, the size of the fish, the location of the fish for an advisory, and when you have 1200 bodies of water that gets you a pretty good sized book and most people just couldn't remember the advisory. It was scientifically consistent with risk numbers but made for

very confusing type of advice.

So, what we decided to do is step back, go back to a somewhat more qualitative approach and look at where do the various fish species fall, and try to come up with some general guidelines for most inland waters. There were some specific hot spot areas, which now comes down to 92, where the data shows that we needed more stringent advice. But, again, when you are looking at 15,000 different lakes, to have a list of 92 it fits on the back of a single page.

[Slide]

So, what we ended up with is not exactly using the FDA. Keeping in mind that we had an advisory, yes, it has to have a science base but it doesn't have to be a strict regulatory application of a number. So, for women of childbearing age and children we went with one meal a week for pan fish, including bluegill and sunfish, and these are what the vast majority of the population catch.

It happened to be trout unlimited, so you see the fly fishing rod here. That is something that a lot of people use when we are trying to encourage that as a sport, especially for women.

[Slide]

Childbearing age women could eat, in addition to the one meal a week, one meal per month of game species, which is walleye, northern pike and the bass species, catfish. Some might argue that a sucker isn't a game species but the size of the suckers in Wisconsin--

[Laughter]

--I am just kidding. Actually, there is a fairly substantial netting season for white suckers. For the others, unlimited amounts of pan fish. If you look at our creel census, this is the class of fish that are low on the chain, they are in every lake and it is something that just about everybody can catch; you don't even have to have a boat. So, this is our number one consumable sport fish.

[Slide]

For those not covered by the women of childbearing and kids, they went to one meal a week for game fish.

[Slide]

And, what we found when we started to look at mercury, and I will give you a little of our survey data on

that and that is what you have been hearing and is perhaps one of the reasons the group is here is, as we began to look at mercury and fish consumption, unlike our other advisories for PCBs and dioxin, PCBs are not a serious or significant contaminant in most commercial species where mercury is quite comparable to much of our sport fish. So, what people wanted to know is, well, how does this compare to fish I buy in the store? If I don't eat walleye and I go and buy Canadian walleye, or I go and buy cod, or tile fish from the store, is that better or am I getting more?

So, we really felt we needed to move into having a combined advisory. Up to this point we had always segregated the commercial fish which are under a regulatory approach from the sport fish which was a strict advisory. I guess because salmon is amongst the most commonly eaten we included that, but you can see it is basically a very low level fish compared to some of the others. You can read here basically what we are saying. So, this is a little segment that is in our advisory, telling people a little bit about it.

[Slide]

One of the things that we are moving towards in Wisconsin and other states as well--the last slide showed you the commercial fish and then you have the sport fish advisory and people want to know, well, how do I combine

these? How does this fit with that one? So, this is from our women and children's guide to eating fish from Wisconsin including sport and commercial. Here we kind of lay it out since white tuna is one of the most common fish eaten and most commonly people will ask, "well, what if I eat tuna too?" So, we have one meal a week of tuna, a 6 oz can being one meal. Then, in addition to that, you could have another meal of a sports species or other commercial fish that you would buy or eat in a restaurant. Then, in addition to that, one meal a month of the sports species and then we list the FDA's "do not eat fish."

Where we are intending to go is to, hopefully, get some additional data, and we may want to add some of the commercial fish into the one meal per month category so that people will understand how it compares to their sport-caught fish.

DR. MILLER: You have five more minutes.

DR. ANDERSON: Okay.

[Slide]

I am going to go quickly here. This is also in the women's guide, some pictures and then you will see the little red, yellow and green spots there by the level of contamination of the fish.

[Slide]

I just want to say that really the advisory program at the state level is a joint activity between the environmental agencies and the state agencies. Typically, the monitoring is done by those individuals in the environment; the health side deals with human monitoring. I am going to show you a little data from some of our other grant-funded activities.

[Slide]

Just to give you a sense of what we do in Wisconsin, our average sample is about 800 fish per year. You can compare that to what the commercial fish monitoring program is. You can see we have a lot of data for a lot of different species and a lot of sites in the state, roughly 2600 samples in our database.

[Slide]

One of the things we found is that if you are a sport fish consumer, on average you will eat about a third or more total fish than the rest of the population. So, there is a reason why you like to fish, you like to eat the fish and, if you are successful, you may have more sport fish in your diet; if you are less successful you may still be eating a lot, supplementing with fish from the store.

[Slide]

For our one survey on mercury, we did a 12-state survey. It is a joint project between Maine and Wisconsin.

[Slide]

Very quickly, what we did was we asked how much fish they ate and here you can see what most surveys find, about 87 percent of people eat fish every year; 13 percent don't eat any fish. So, fish is pretty big. You can see 3000 women we surveyed had reported eating sport fish, but the vast majority of the fish eaten was fish fillets and tuna.

[Slide]

This jut shows the meal per year. Again, fish and tuna is the predominant number. The average of sport fish, of course, is four. if you say, well, 25 percent of the people are eating that, you multiply that by 4. If you are a sport fish eater, you are eating like 16 meals a year.

[Slide]

This just shows you there are differences by state. The red dots are pretty even between the states but you can see sport fishing consumption varies from a low of 10 percent to a little over 40 percent in the group.

[Slide]

We asked them what do they know about mercury. They did real well on recognizing the hazards, that it harms a developing child. So, we thought, gee, they have pretty good information.

[Slide]

Where we fell down is that we have been too successful with our PCB long-term lipophilic chemical advisories saying remove the fat, get rid of the skin and you will reduce your exposure by 50 percent. So, the women said where do you find mercury? In the fat? Wrong. Where do you find it? You find it in the muscle. So, if they thought they were protecting themselves from mercury by removing the fat and skin, it is a misperception.

[Slide]

This is no news to most of you but, again, where do people get their information? You can see that government is right down at about eight percent. In fact, we haven't gotten much information out to physicians as they are a little lower than government. So, we have a long way to go. If you think what you are doing here is going to reach people, you are going to have to have a pretty aggressive program.

[Slide]

This just shows advisory awareness. We chose states that all had advisories, different types of advisories, but here you can see we really are not doing too well getting the women to even know their state had an advisory. Every state had an advisory. Fortunately, Wisconsin and Maine were leading the charge and had the

money to put more information out. Arkansas also had a new initiative, and Minnesota. We were on the top end of the list but you can see states on the lower end have a pretty random chance that the women--they may have been trying to please us by saying, "oh, yes, I know we have an advisory."

[Slide]

We asked for women to volunteer to send in hair for analysis. Over 80 percent said yes. When they got the packet of what they needed to send in, participation fell off but actually it was fairly representative. This just gives you the distribution of the hair mercury levels. The highest we had was 4.6.

[Slide]

When we looked at what they ate and what their hair mercury levels were, this is just how much they ate not looking at interactions here, the best predictor of their hair mercury level was total fish consumption. Interestingly, shellfish came up second. That should be tuna and other fish fillets; sport fish and then the state advisory sport fish that specifically were covered by the state as either "do not eat" or a severe limitation and there wasn't much of that fish being eaten but, again, you can see it was significantly correlated but not as strong as total fish consumption. So, you can see why we need to

include all fish if we are giving advice and not just focus on the last two columns.

[Slide]

I am reluctant to do this because the strength of the NHANES is far superior to our methodology, but everybody wants to know how does our distribution compare to the national average. You can see our sample falls pretty much within their confidence limits within the various percentages.

[Slide]

Our recommendations are we really need to have more information on commercial fish monitoring, and it needs to be not designed from a regulatory standpoint but from an advisory standpoint. Can we place fish into various groups? We need to increase human biomonitoring. The RfD is in micrograms per kilogram per day, and how do we then convert that back to humans? Well, it started from a bench mark of 12 ppm in hair. So, we converted to human data into a micrograms per kilogram per day data and then we convert it back if people want to know levels in hair and blood. It is relatively inexpensive. It is a test that can be done and we need more actual, real-world measurement data for targeted populations.

We need to do more health research. The adult population has been left out of this. We have focused all

these large studies on kids. We do know that mercury is likely to have adult effects. We have adult data. Those of us who have split advisories, we use the adult data from the Iraqi study, if you remember back in the '70's. That is about the only human data where you can do methylmercury dose response information on health effects, and that is pretty poor. So, we need to have better data to address the predominant population which is noon-pregnant, non-kids.

[Slide]

Lastly, what we need is state-specific integrated sport and commercial advice. While it is helpful to have FDA give advice and do measurement, I would say right now those states that are issuing mercury advisories are recognizing that we have to have integrated advice. The best place to issue that integrated advice is at the state level. So, we need to have greater integration and coordination between federal and state agencies. Again, the key thing is to get, whether it is negotiated or otherwise, uniform consumption advice. It has to be able to include site specific information that states have; fish that don't move around; fish that are different. But for fish that are in the commercial market, we need to have those so that we can add those into our comparative database.

Another issue that needs to be looked at special circumstances. They may support a need for reduced margin of safety. In other words, the RfD has built into it an uncertainty factor of ten to accommodate adults as well as other potential health effects but, again, in special circumstances it may be an appropriate public health activity to accommodate a slightly lower, say a factor of five, in that process because of the local circumstances.

Again, the goal is to eat the same amount of fish you always ate but select fish that are low in mercury. That is the advice and information in Wisconsin we started with in the '70's. We are now back to focusing more on that and less on the risk assessment.

[Slide]

This is what we have distributed to all our physicians. We decided that rather than to going with a detailed advisory, our public relations people said go with a two-stage message. Give them something that they like. It is a poster. This is also on cups. We have sippy cups for moms. We have growth charts. We have refrigerator magnets. They are all saying here is where you call. Get them interested and they call and they can get the additional information. So, most states that had low budgets could only go with putting a little advice out to the angler in the fish advisory or in the fish regulations,

and we found that mostly the guys who were fishing, they brought the fish home and said "cook it," and the information never got transferred over. So, we are now targeting specific information to specific populations.

[Slide]

Again, "come to Wisconsin and fish." These are not fish you are going to eat but these are fish you are going to get--

[Laughter]

These you put on the wall.

DR. MILLER: Are you about finished?

DR. ANDERSON: I am done; that is it.

Questions of Clarification

DR. MILLER: Thank you. I was wondering if there were any more advertisements that you had!

[Laughter]

DR. NORDGREN: I would be interested in the variation you did have within species and different sites. We don't need a long expose but, obviously, there are variations at various sites within the same species in Wisconsin.

DR. ANDERSON: In general, the range is about an order of magnitude, maybe 20. We no longer have many fish over 2. Now, the fish that are over 2 I would say are trophy fish and nobody is catching enough of those to eat

enough of them. There are some, like the big muskies, that can get old and will have higher levels but most of the fish fall into the 0.2, 0.161 to 0.5 range. The 92 lakes that are over that average over 0.5, lakes and river stretches, and those are the ones that we have more restrictive advice on. So, the fish are pretty tightly bunched. I would say much more bunched than they are on the commercial side.

DR. MILLER: Dr. Dwyer?

DR. DWYER: Just two things. I really like the integration of the message on the sports fishing and the commercial together for the consumer. I thought that is really great. But just carrying it a little further, remembering my own time in Wisconsin and seeing people fishing, have you ever thought of incorporating alcohol use advice? Sorry!

[Laughter]

DR. ANDERSON: There is lots of public health advice. I am here, talking fish today. We have a big alcohol program. One of the most effective tools for alcohol regulation on the lake is wardens, and you may no longer drink and drive. Driving includes boats. So, if you happen to be stopped throwing a beer can over, that is a $250 fine for the can. If you happen to be over the drunk driving limit, you lose your boat as well. So, that

doesn't necessarily stop anything but it is a fairly powerful incentive to pay attention.

DR. MILLER: Dr. Aposhian?

DR. APOSHIAN: I was interested in your asking people, or women I guess, where did you learn about methylmercury in fish. Also, I could read your advisories very well. I want to compliment you on that. Why doesn't the State do anything about distributing the advisory to pregnant women, like making copies and putting them in obstetricians offices?

DR. ANDERSON: Well, we have done that. Thank you for reminding me.

DR. APOSHIAN: Because one of our problems is, and I think the committee agrees, trying to get this information to pregnant women and women of childbearing age.

DR. ANDERSON: This is our little women's guide to eating fish in Wisconsin. I will hand it around. That has gone out. The second to the last little poster there was specifically distributed to all physicians' offices. We try to encourage them to have a kind of a public health display where they have vaccination information and STDs, along with now a poster and the fish advisory.

Our major emphasis right now is with the WIC program. Forty percent of the pregnancies in Wisconsin go

through the USDA WIC program. That is a dietary program, and they have all of the materials as well, as I say, the refrigerator magnets, T-shirts, sippy cups and things like that. So, we are now in the process of another survey in the field to find out if we have raised the awareness, as is Maine with a little different program, just to see whether we can do that. We are trying to get more information out and get it distributed to the individuals that need to know.

DR. APOSHIAN: May I ask one more question? I know Wisconsin has always been a very progressive State and certainly many of us admire both the health and educational benefits of living in Wisconsin. I am impressed that you have done so much with sport fish. Does your State do anything about analyzing commercial seafood? Does it analyze cans of tuna fish for example? Or, do you feel that is not within your jurisdiction?

DR. ANDERSON: At this point in time we have not done it. All of the targeted commercial fish is for regulatory purposes. I think we have a few commercial fishermen still in the State. So, our department of agriculture will monitor the whitefish, the smoked chubs, but largely they are targeted, as you saw the FDA program, on fish that they may need to take out of the marketplace. So, at this point we are not doing commercial. If we have

to, we will move into doing that but right now the dollars for the screening programs come from the licenses that anglers pay. They don't really want us to use that for other food safety issues.

DR. APOSHIAN: If I understand it correctly then, you take the advice the FDA gives you on commercial fish brought into the State of Wisconsin.

DR. ANDERSON: Yes, they are the regulators of commercial interstate transport.

DR. APOSHIAN: So, it is the FDA and not the Department of Agriculture? It is the FDA that you depend on?

DR. ANDERSON: I believe the State may implement, but the regulatory underpinning is our FDA.

DR. APOSHIAN: Thank you.

MS. HALLORAN: In preparing this very good brochure, did you look into PCB levels in fish and consider them?

DR. ANDERSON: We also have PCB information but this was specifically focused on the mercury issue. You know, we have been beating on PCBs a lot longer. Most of the mercury fish are not high PCB fish. Mercury is an inland lake problem; PCBs are a Great Lake problem right now, except for a few areas with paper mills on the river. But we are trying to integrate the general advice. Some of

the fish get in different places because of PCBs, some are there because of mercury. We take whichever is the most conservative advice even though we are not sure that the two have the same mode of action for the advice. So, we are trying to combine it.

MS. HALLORAN: So, in terms of the fish you are recommending, those are all okay in terms of PCBs?

DR. ANDERSON: These would all be consistent. If you used PCBs for the advisory, they would be consistent with it. Mercury happens to drive these. All the pan fish are very, very low in pesticides.

DR. MILLER: Dr. Fischer?

DR. FISCHER: Henry, could you tell us a little bit about the human monitoring effort that Wisconsin is doing or planning? I think you mentioned that, didn't you?

DR. ANDERSON: Yes, we have several projects under way. The one I talked about is the 12-state survey. We also have an indicator project that is being implemented in WIC clinics along the Great Lakes to give dietary histories of fish consumption, hair samples and to a lesser degree also look at some PCBs so we can look at an age-specific group over time because if the levels are down we don't know if they are down because of following the advisory or because the levels are lower in the fish. So, we are trying to tease that out in this population.

DR. FISCHER: These are done in the research mode as opposed to surveillance?

DR. ANDERSON: These are done under a public health surveillance mode because it is part of our advisory information. It is being implemented under our statutory authority to monitor the general population, just as we do lead poisoning.

DR. MILLER: Dr. Scherer?

DR. SCHERER: I was just wondering. In your little brochure here you have swordfish and shark marked as "do not eat." Then, over on the other side you have northern pike and walleye that are also high but no indication of concern. In looking at it, that seems inconsistent from a consumer point of view.

DR. ANDERSON: Well, if you look at the first thing, the tear-off, all of those fish are in the one meal a month. Those are the game fish.

DR. SCHERER: Okay, but the inconsistency is that they are also indicated as high, and are red in the chart, as are the two that say "do not eat."

DR. ANDERSON: The "do not eat" have Xs through them. You don't know how long it took and, you know, we worked with Maine and they use a thermometer, and our thermometer people were upset that we are using a thermometer to give how high it is.

[Laughter]

Then it had to be quantitatively similar. This one, even though it doesn't say it, must be 0.1 and that must be 0.6. There are so many ways you can do it. Again, what we did with this is take it out to women at the WIC clinic and ask if this makes sense to them. How would you interpret it? If they were comfortable with it, even if our science folks were a little miffed, we went with the people whom we wanted to reach.

DR. MILLER: Other questions? Dr. Fuller?

DR. FULLER: I just want to clarify and follow-up on a question because I don't recall from your talk, were the concentrations in the pike and walleye comparable to the concentrations that are X'd out, the swordfish and the shark?

DR. ANDERSON: No, they are lower.

DR. FULLER: Thank you.

DR. ANDERSON: On average. What we tried to do is look at what are people actually catching, and if there is a fish there that you shouldn't eat but nobody has caught one, you know, why issue advice to not eat it? That is sort of the way we went. So, the two that I showed at the end, they are "do not eat" not because of the mercury but because of the PCBs, but they are nice fish.

DR. MILLER: Dr. Lee?

DR. LEE: There seems to be somewhat of a tradition in Wisconsin to eat fish on Friday. I was just wondering have there been any attempts to getting this kind of information to point of consumption, particularly in restaurants, and do we have any wild guess as to how much exposure might come from restaurant fish in Wisconsin?

DR. ANDERSON: No. Restaurant, we call that commercial fish. When we ask people, "so what kind of fish did you eat?" Most people don't know. They would be able to say it was a shellfish or shrimp or it was a fish, and it was a white fish or it might have been a darker color. They typically know salmon because salmon is pink. They know trout because they come with a head on them.

[Laughter]

But other than that, you have a standard fish in the restaurant, and you don't know what it is or where it came from so we just count those as fish meals. We tried that and nobody knew.

DR. MILLER: Other questions? Dr. Dwyer?

DR. DWYER: I was just wondering, I know we have a lutifisk expert over there but where does that fall?

DR. ANDERSON: Where does what fall? Lutifisk? Lutifisk is low, high in sodium--

DR. MILLER: Low in taste.

DR. ANDERSON: High pH.

DR. MILLER: I was tempted to indicate that at least your people seem to know what a fish is!

[Laughter]

DR. ANDERSON: We don't have to deal with a dolphin fish versus a dolphin and those kinds of things.

DR. MILLER: And tuna fish! All right, thank you. We are going to take a break and be back at 3:15.

[Brief recess]

DR. MILLER: A couple of things before we begin the afternoon session. I would appreciate it if anybody who has an active cell phone, if they would put it on silent, vibration or whatever. When it rings it tends to interrupt the discussion. The second thing is for Dr. Aposhian.

DR. APOSHIAN: This morning Kate talked to you about the work of the NHANES. She brought today a group of papers that she thought the committee would like that, hopefully, have been distributed to you by the FDA staff, dealing with possible relationship of mercury levels and coronary heart disease and other cardiovascular problems that have appeared in peer reviewed journals and she thought might be of interest to you.

DR. MILLER: And we can consider that as part of the EPA presentation. Our first speaker this afternoon is Mr. Michael Bender, from the Mercury Policy Project. He

will talk about mercury contaminated seafood state advisories and other protective steps.

The Mercury Policy Project

MR. BENDER: Thank you, Mr. Chair. Good afternoon. Before beginning, I would like to, first of all, express my appreciation to Mr. Joseph Levitt for inviting me here today. I didn't realize that I was going to be presenting at this meeting until just very recently, and so I apologize for maybe not being so well versed in my homework assignment.

DR. MILLER: Excuse me, could you adjust the microphone so you can talk right into it?

MR. BENDER: Of course. Again, I apologize for not maybe being as prepared as I could. I did the best that I could under the circumstances.

I am pleased to announce that we recently got a bill out of the U.S. Senate Environment and Public Works Committee that will ban the sale of mercury fever thermometers. There are ten states nationally that have done this and everyone else went on vacation. It is sort of like you are in a line and everybody else steps back and you realize you have been volunteered. So, I spent a number of days having to deal with that situation, but it was well worth it and we will keep our fingers crossed.

In any event, also in addition to expressing my appreciation to Mr. Levitt, I have a packet of information for all the committee members. Included in that packet is joint FDA-state conference call minutes that I put together prior to the issuance of the consumer advisory in January of 2001. Also in that packet is a briefing statement that perhaps you might have seen from the National Fishery Service. It is very specific to this issue. Also, my presentation.

The reason why I mentioned in particular the state-FDA minutes is because even though I commend the organizers on the depth of this meeting, and I was very pleased to see Dr. Henry Anderson here, and I recognize that some of the panelists are from the states, I would just submit that the states that are involved in this issue should also be heard and a number of them have emailed me, and I will do my best to convey some of that information from the states, but the minutes speak for themselves. They are also on our web site.

[Slide]

To start, the Mercury Policy Project is a nonprofit project. We are dedicated to reducing human exposure to mercury. We are also dedicated to reducing man-made mercury uses and emissions. For more information

about our work, I encourage you to visit our web site at www.mercurypolicy.org.

[Slide]

I apologize for the resolution of this slide. It is on our web site. It is part of a report that we released in 2000, and it was based in large part on an FDA data set from 1992 to 1998. One of the first things that jumped out at us was that we were startled to discover that FDA hadn't tested canned tuna since 1995. The data set also revealed--although you obviously can't see it here but it will be in your packets and you can see it later--that in addition to the shark and swordfish some tuna, the large tuna exceeded FDA's 1 ppm action level.

[Slide]

While we were working on this issue we were noticing that the southern states were very active regarding the issue of king mackerel. Leading up to 2000, when they issued their joint advisories, they had issued individual state advisories. One thing I really would like to point out is that these advisories really pay attention in the testing and sampling to the size of the fish. It is a very important point. I was recently at a meeting in Mobile where the southern states and also EPA, and I believe, National Marine Fishery co-sponsored that meeting. When we do our fish data, it is very important to also be

tracking size of fish so that we can make a correlation between the size of the fish and the amount of mercury to provide more accurate warnings.

[Slide]

So, in addition to the king mackerel, as I said in the beginning, a considerable number of states have issued commercial seafood advisories. To a large extent, these advisories are more stringent than FDA. I am sorry this graph isn't all that clear, but for children under six, eight or whatever it might be, for the large tuna Connecticut, Massachusetts, Minnesota, Washington State and Wisconsin all advise children to limit or not consume fresh tuna.

A number of states, including New Jersey and Florida, have conducted their own mercury seafood testing. Minnesota is actively testing and enforcing FDA's 1 ppm standard and, in effect, is not allowing fish exceeding the FDA's action level to be sold in the state. Here you have a state that is literally interpreting the FDA guidance and whenever shark or swordfish are brought in the state, the state has a very aggressive program. They go out, they test the fish and pretty much those fish aren't being sold in the state because they predominantly exceed the 1 ppm.

In addition, the Mobile register in Alabama recently tested and found that many seafood, including

black grouper, red fish, cobia, amber jack and triple tail may have average mercury levels greater than 1 ppm, although it is a very small data set.

Due to the issues raised in the Gulf, and recently President Bush initiated an international mercury task force related to oil rigs and mercury contamination, the National Marine Fishery Service and EPA plan to carry out a sampling survey over the next year to analyze 2500 popular marine and recreational seafood fin-fish for mercury.

[Slide]

One of the focuses in the southern states is fish specific to that region, but why are we so concerned about canned tuna and the general population? One of the reasons is because if you look, and although this is 1997 and the source is the annual report of the seafood industry, one of the largest consumptions, average consumption, is the home canned tuna sandwiches. In addition, in the June 2001 issue of consumer reports, there was a statement in there that canned tuna may be the only seafood that many children eat.

[Slide]

While there is a general lack of current data on mercury levels in canned tuna, we combined the data sets, the earlier one which you can't see, from the FDA and it

took us two years to get that information by FOIA, and the Florida data from 1990 and 1991 and another data set in Florida in 2000, which is actually on the FDA's web site now.

What these samples indicate is that there are quite a number of samples over 0.3 ppm and in some years upwards of 10 percent are over the FDA's action level of 0.5 ppm. Those are the references where some of this data came from. I understand that there was a '92 year study which was a far greater sample size and indicated I think an average consumption of 0.17.

What concerns us from a public advocacy standpoint is that people don't eat averages. I am not quite sure how the average rationale comes around, but I find that very problematic when it comes to sensitive populations.

[Slide]

When we look at what is going on now with the states, starting in 1997 and some of these dates might not be exactly right but we did the best we could in less than one week in gathering information from the states. We had our own file plus some of this information that is now available on the EPA's web site under commercial advisories that the states are issuing. But if you look right down the line, what we are talking about compared with the FDA

which is 12 oz of canned tuna per week, the states are coming in at a much more cautious level. It really varies, but, as you can tell, there is a real trend now where I guess because we don't have data--I think that is one the biggest problems that we have, the biggest challenge that we have right now that there is so much uncertainty out there that the states are saying, based on what the NAS said, we need to take a more prudent approach.

[Slide]

I apologize for this slide. Actually, the one I wanted to highlight is the marlin. This is the recent data set from the British Food Standards agency which issued a consumer advisory for pregnant women, women who intend to become pregnant, infants and young children under 16 years of age. In addition to a recommendation that they avoid eating shark and swordfish, they also recommend that they avoid marlin as well.

According to the British agency, and this is right off their web site and I am quoting, these seafood can harm the nervous system of an unborn child if the fish is eaten regularly by its mother. Infants and children may also be at greater risk for mercury poisoning because they eat more food relative to their body size in comparison with adults, according to the agency.

[Slide]

So, just to wrap up here, in terms of recommendations and these really build off our earlier recommendations in our "One that Got Away" report in the year 2000. First of all, FDA should develop effective surveillance, monitoring, testing, enforcement and consumer programs for methylmercury in commercial seafood in conjunction with consumer groups and the fishing industry and appropriate federal, state and local government agencies.

Part or the rationale, as I mentioned in the beginning--I only spend a certain amount of my time in trying to raise awareness about the need to reduce human and wildlife exposure to mercury. Much of my time is spent on efforts at the state and national level to reduce and eliminate man-made mercury emissions. Actually, I am pleased to say that the United Nations is doing their first ever global assessment of mercury. I will be representing the NGOs from the northern countries in Geneva in September, and will be working on recommendations to the governing counsel at their meeting, in Nairobi, in February.

So, we are seeing our state and local governments and our federal and state governments spending millions of dollars each year tracking every other aspect of the mercury problem. Yet, how can the U.S. measure meaningful

progress in reducing mercury pollution over time if we are leaving out testing one of the most critical indicators, methylmercury levels in seafood? I think as most of you are aware, that is the predominant fish source for most Americans.

Secondly, some of the existing federal and state data for mercury is decades old and needs to be reevaluated for accuracy and applicability in the light of modern state-of-the-art testing methodologies, approaches and equipment.

Also, critical fish size data, as I mentioned earlier, was not incorporated into those data sets, and it must be included as part of any comprehensive seafood testing and monitoring program for methylmercury.

Finally, and this is just my first recommendation, while the National Marine Fishery and EPA are on the verge of testing popular marine and recreational fin-fish for methylmercury in the Gulf, their primary intent does not appear to be testing methylmercury levels in commonly available, commercially harvested seafood species. That is according to the March 27, 2002 National Marine Fishery's briefing statement which you will see in your packet.

[Slide]

In light of the most recent science, FDA should establish a regulatory level for methylmercury that is fully protective of the U.S. population and, in particular, women of childbearing age, pregnant women and nursing mothers and children.

Also, FDA should expand its list of "do not consume seafood known to have high mercury levels." The rationale? In the past FDA has all but ignored the findings of the 1991 studies by the National Academy of Sciences and the U.S. General Accounting Office, and one wonders aloud if this will happen again, history repeating itself.

For over ten years FDA has been evaluating the hazards of mercury in seafood but has never issued the results. In 2002 GAO released the report on the inadequacy of FDA's hazard analysis critical point regulations. According to GAO, FDA does not provide adequate guidance to the fishing industry to identify and prevent seafood contaminated with methylmercury from exposing consumers. GAO recommended that FDA complete its hazard assessment for mercury in seafood soon.

The third point, the July, 2000 NAS report endorsed EPA's reference dose, as has the European Union. As I have mentioned earlier, this issue is getting more global in scale every day and it is a welcome sign because

the United States has to play a leadership role internationally if we are really going to address the problem. Because the fish that we are catching are from the open seas we need a global solution to this problem.

As also discussed, 20 percent of the state health departments in the nation appear to be applying some variation of the NAS approach to advise sensitive populations about methylmercury in canned tuna.

I don't mean to harp on canned tuna. There are a number of other fish that have levels very comparable to this in terms of the risk factor for sensitive populations. In addition, there are many commonly consumed seafood, including but not limited to marlin and tuna, and indicators from the Mobile register testing clearly exceed the FDA's current action level at least part of the time. Again, people don't eat ranges; people eat individual servings of fish.

[Slide]

Finally, our recommendation number three, FDA must recognize, as does the National Marine Fishery Service now, based upon a briefing statement I mentioned earlier, that, quote, subsistence commercial and marine recreational fishermen and their families represent a new subpopulation of the seafood consuming public that will likely require

additional safeguards in order to protect them against excessive methylmercury ingestion via seafood.

Again, according to the briefing statement of the National Marine Fisheries, there is a portion of the public that consumes seafood in excess of 15 lbs per year, and they also consume large quantities of seafood that are harvested for personal consumption. In particular, subsistence commercial and marine recreational fishermen and their families are at risk of exceeding the methylmercury consumption guidelines as they may be consuming seafood well in excess of 15 lbs per year, and they may be consuming non-commercially harvested seafood that is not subject to the FDA's 1 ppm methylmercury monitoring restrictions.

I guess, in closing, we have been around the barn on this issue for several years. There are major inconsistencies between what the states are doing, what FDA is doing, what EPA is doing, what ATSDRs MRL are. Members of Congress have written letters. We have had meetings sponsored by the White House to address this issue.

I think when it comes down to it, I guess the main point I would like to leave you with is that there are uncertainties and there will remain uncertainties. The reason the mercury study report to Congress got held up for three years, from 1994 to 1997, was over this issue. And,

part of what it is about, it is about a number of different business groups weighing in. It is about government agencies weighing in and all the rest.

But I guess I would go back to what I said in the beginning. Without adequate data, I think we need to do something similar to what they just did in Britain. They issued some kind of interim advisory. I asked FDA to do this a few years ago. I said let's set something in place. Well, we don't want to do that because, you know, all of these reasons. Let's set something in place, and part of the reason is because we need to protect those populations and we don't know whether we are or not.

The other part of the reason is if we set something in place, I can assure you it would be a very strong impetus for all the parties involved to want to support having FDA and the other federal and state agencies going out and doing those tests and coming back with the data and monitoring the political pressure that it is going to take to convince Congress to allocate the funding for FDA to do an adequate job in this area. Let's come back in a couple of years. Let's issue some interim advisories that are more consistent with where the states are as a prudent public policy approach, and then let's get FDA the money to do its job, mandated by Congress.

Everyone wants the answer. I just got a call from a reporter, and I don't know if the gentleman is here, from a Pittsburgh paper. They want to duplicate the Mobile register findings and it is beyond my comprehension that we have to have newspapers in this country performing the role that government should be performing. Thank you.

Questions of Clarification

DR. MILLER: Thank you. Comments? Questions?

DR. NORDGREN: I couldn't read the ranges in the English study. Could you go back to that slide?

MS. DEROEVER: Dr. Nordgren, could you please use the microphone?

DR. NORDGREN: I couldn't read the ranges in that English study.

MR. BENDER: I could pass those out if that would be helpful to the committee, Mr. Chair.

DR. MILLER: Yes.

MR. BENDER: Can I pass out the information that my slide wasn't able to convey?

DR. MILLER: Of course.

MR. BENDER: The pages aren't numbered, I apologize. It is after the mercury and tuna methylmercury advisories. It is titled, mercury levels in fish, shellfish, a recent survey. The mean is 1.091; the range

is 0.409 to 2.204. Again, the sample size is very small, only four samples.

DR. NORDGREN: One other question, milligrams per kilogram, how does that come out in parts per million?

MR. BENDER: I would have to defer on that to someone else.

DR. MILLER: Other comments? Annette?

DR. DICKINSON: You indicated that you thought FDA should set an action level for fish that is consistent with the EPA RfD. What would that number be, in your opinion?

MR. BENDER: Actually, first of all, I would just like to say that I don't think that FDA should go with an action level anymore. They need a regulatory limit or we are going to be in waffle-land for the next twenty years. With all due respect, I think that is a problem.

When I had asked FDA a few years ago when we had the meeting with the states and Mr. Levitt on the phone, what I said was can we have two approaches, one for the general population and one for sensitive populations? That is what most of the states are doing right now because we don't want to discourage the consumption of fish. There are many species out there that are very low in mercury. Salmon is one of my favorites.

What we want to do is get the message to the populations most at risk until we have enough of an adequate data set to be able to have a more accurate read of what is going on here. If we are seeing a data set like the one out of Florida where they were up at something like 0.24 ppm on average rather than 0.17, I think that really requires some rethinking of FDA's approach.

But, yes, I don't have a science background so all I can say is based on what the experts I speak with say, and most of the experts I speak with are state health department officials, and that is what I work with. Unofficially, that is my team on this issue. I used to run a state and local government association and I feel very comfortable working with the states. I feel very comfortable working with the experts in this area. As I said in the beginning, I am just disappointed that there aren't more state health department officials here.

DR. DICKINSON: Mr. Chairman, the EPA speakers are still here, I think, in the audience. Could we ask them what they believe a translation would be of their RfD number into a general action level or regulatory level for FDA?

DR. MILLER: Yes.

DR. DICKINSON: We have had some people talking as though the 0.1 ug is how it would work out in fish, and

I wonder if we could hear from EPA whether that is how they would interpret that.

DR. SOUTHERLAND: I will refer you back to the table I had in my presentation. It depends on the number of fish meals that you are concerned about in terms of what that equates to in terms of concentration. I think that is what you are asking, what fish tissue concentration of methylmercury would we recommend for an action level or tolerance level. Joe?

MR. LEVITT: We are going to be addressing that tomorrow morning.

DR. SOUTHERLAND: But I would refer you back to that table. It depends on what you are looking at in terms of fish meals that you want to recommend because the RfD multiplied by the number of meals that you have gets to the concentration that you are concerned about. That is why on our table we showed you varying concentrations that go from 0.1 to 0.9, depending on what number of meals you think are appropriate.

DR. DICKINSON: Right, and that may be relevant to a consumer making their own judgment about what they are eating and how often they are eating it, but from the point of view of just wanting a number to apply as a regulatory matter--I realize we are going to her from FDA on this tomorrow but I don't know if you are going to be here

tomorrow. I just wondered what FDA's interpretation would be when someone says you should use the RfD as the basis for a number. What does EPA think that would mean?

DR. MAHAFFEY: Kate Mahaffey, EPA. One of the complications in this is that there are a number of nutritional messages, including American Heart Association which says we recommend you eat two fish meals a week. So, if you take those kinds of recommendations and translate this to some estimate of the quantity of fish it should represent and take a look at the reference dose, you can sort of back your way into a level that we would believe would be safe.

Now, part of the dichotomy here is that things like the American Heart Association recommendations are primarily aimed at another age group. So, how you translate this between avoiding cardiovascular risk and, yet, being protective of the developing fetus is one of these judgment issues that needs to be data driven, but it is one where we have a lot of factors to consider.

DR. MILLER: We will discuss that at greater length tomorrow.

DR. KUZMACK: Arnold Kuzmack, EPA. One brief additional comment is when you are talking about an action level you are talking about a level at which you would

seize the fish, which is different from the level that you think is allowable in fish.

DR. MILLER: All of these have been recommended by one person or another for action, so it is important to get these numbers to make sure we all understand exactly what these numbers represent. So, we will discuss this at greater length tomorrow.

DR. KUZMACK: In order to come up with anything meaningful, you can make some additional policy judgments.

DR. MILLER: A very straightforward policy, as many people have said is, well, let's eat salmon because it is low in mercury. But what happens if it turns out that salmon is high in some other contaminant, fat soluble contaminant?

DR. KUZMACK: That is a good point and I do think that even though I work on mercury policy issues, I have been around long enough to recognize that you need to have an integrated message. How many messages can you send out and have the public receive at one time? I am not a professional risk communicator here, but it is obviously something that those folks need to be looking at.

DR. MILLER: That is clearly going to be the challenge.

DR. MCBRIDE: How is the Mercury Project funded?

MR. BENDER: By foundations.

DR. MCBRIDE: What type of foundations?

MR. BENDER: I don't understand the question. What do you mean?

DR. MILLER: I am not sure that that is relevant for discussion. I don't think it is important to this issue. Dr. Dwyer?

DR. DWYER: Thank you for an interesting presentation. I was a little surprised--I have been surprised all day about many things, but particularly about the number of samples that are around where people have looked at fish, and there are databases I just didn't know about, state databases, some of the EPA and other databases. Then, I also hear in several presentations people saying there aren't enough values; we need to get more; do more. Is the problem that it is not a random or representative sample? You mentioned in your presentation, I believe, that they were doing work down in the Gulf where they are picking samples but they were picking them for another purpose. Is there a way to have a subset of those fish that are being analyzed? Can we somehow get a sampling frame that would give us data that would be more meaningful for human consumption?

PARTICIPANT: [Not at microphone; inaudible].

MR. BENDER: Right, but that is recreationally caught, not commercially caught. Whenever we present ideas

like this to federal government agencies part of the challenge we run into is whether or not those federal agencies are willing to accept that data. When we provide them with information, the question back is, is this peer reviewed information? So, I think just by its very nature of where we want to end up with the federal agencies, it really has to have their blessing in terms of how we go about doing it, and they have experts that understand sampling size, methodologies and testing. I mean, they have a whole section in their agency that is involved with looking at that.

So, yes, I guess the simple answer to your question is, yes, we could compile that information. The question to FDA is would you use that information? Would you be willing to use that information? I am sure the response back is, well, it depends.

DR. DWYER: Well, I think it does depend. At least, we need to know where the samples came from; we need to know the analytical method and so forth. You know, just throwing numbers at problems doesn't get very far. But the question is are those data collected in a good way. If they are available and a complete description can be made of how they were collected, it may be not necessary to do a whole bunch of new data.

MR. BENDER: If I could, I will just reiterate what I said earlier. It took us two years to get that 1992 data, which is the second slide in your packet. The little story on that is we FOI'd FDA. We got a very concise range of numbers. Then a reporter FOI'd FDA and they got that huge data set of hundreds and hundreds of data entry points.

So, I think one of the challenges in terms of something like that is that the FDA, in my experience, has not been forthcoming in the past in terms of wanting to share that information. We always have to, you know, go through the Freedom of Information Act to get it. Unfortunately, I don't really understand what the relationship is between the states and the FDA. I understand that some of the states do the testing for FDA, but I don't have anything that I can site for you.

DR. MILLER: Other comments or questions?

DR. DWYER: I have one other question. Is it true that king mackerel is king fish?

PARTICIPANT: Yes.

DR. DWYER: I am making a little vocabulary here!

DR. MILLER: Thank you very much.

MR. BENDER: Thank you very much.

MS. DEROEVER: Mr. Chairman, I have a brief statement to make. We do have Dr. Connor on the phone. I

think there was a lot of noise and people may not have heard that. Mr. Collette is going to making the initial presentation--

DR. CONNOR: Hi.

MS. DEROEVER --and Dr. Connor is going to be helping out with some questions.

DR. MILLER: I think we better tell Dr. Connor he is coming through loud and clear!

[Laughter]

MS. DEROEVER: It has been reported to FDA that both Mr Collette and Dr. Connor do have financial associations with the seafood industry, for the record.

National Fisheries Institute

MR. COLLETTE: Good afternoon, Mr. Chairman and committee. I am Bob Collette, vice president of science and technology for the National Fisheries Institute. As has been said, Dr. Connor, who is collaborating on the presentation, is joining us via a telephone conference call.

[Slide]

For the committee's information, the presentation is a collaborative effort between NFI and Dr. Connor, who is a medical doctor and researcher currently affiliated with Oregon Health Sciences University. Dr. Connor has been teaching and conducting research in the area of

clinical nutrition and lipid metabolism for over 40 years, and is particularly well qualified to review the current scientific body of information on the positive health benefits associated with fish consumption.

For your further information, the National Fisheries Institute is a nonprofit trade association representing the commercial fish and seafood industry. NFI is located in Arlington, Virginia and has been in existence for over 50 years.

[Slide]

The purpose of this presentation is to discuss the strong positive role fish and seafood has on the nutrition and health status of U.S. consumers, and to ask the committee and ultimately FDA to carefully consider the possible negative public health impacts should these benefits be diminished as a result of reduced fish consumption.

[Slide]

NFI believes FDA acted responsibly in developing its fish consumption advisory. It was a deliberative process including scientific information from the scientific community, consumer groups, health organizations and the seafood industry.

NFI recognizes that FDA's national fish consumption advisory is an important tool for ensuring the

protection of sensitive consumers. In recognition of the importance of the advisory, NFI has created a direct link to it in the consumer section of our NFI web site. The consumer section is called aboutseafood.com.

NFI also believes that fish is an important part of a healthy diet for many consumers, therefore, government agencies must have sound scientific justification before they tell people to further limit the consumption of fish. Decisions about protecting consumers, therefore, must be based on a thorough assessment of scientific data and the public health impacts, both positive and negative.

In order to make the comparison, we thought it useful to review what specific benefits could be lost or diminished and what nutritional consequences might occur if an expanded advisory were issued and resulted in a decrease of fish.

[Slide]

Fish provides comparable amounts of protein but for most species contributes less fat, calories and particularly saturated fat when compared to other animal protein foods. Fish are a good source of most B vitamins and vitamin B12, which is not obtainable in vegetable products, and only animal proteins, found in fish in large quantities. Fish products, particularly tuna products, are

also excellent sources of selenium, an important dietary antioxidant.

[Slide]

Because fin-fish products contain substantial amounts of protein and relatively low concentrations of fat, saturated fat and cholesterol, health professionals, as part of a heart healthy diet, have promoted consumption of these foods. Indeed, both the American Dietetic Association and American Heart Association recommend consuming at least two fish meals per week, as we have heard already a couple of times.

When AHA released its dietary guidelines in the fall of 2000, they said because of the beneficial effects of omega-3 fatty acids on the risk of coronary-artery disease, as well as other diseases such as inflammatory and autoimmune diseases, the current intake which is generally low should be increased. At least two servings of fish per week are recommended to confer cardioprotective effects.

The AHA statement provides a good segue to Dr. Connor's review of the scientific literature. I want to quickly point out that fish and shellfish are far better sources of omega-3 fatty acids, particularly EPA and DHA, than other animal sources.

[Slide]

The following portion of the presentation really is what constitutes Dr. Connor's scientific review and, had he physically been here, this is what he would be covering.

[Slide]

Interest in the n-3 fatty acids began some thirty years ago in Greenland Eskimos when it was discovered that coronary disease, diabetes and cancer had a remarkable low incidence in this population. Eskimos at that time lives on seafood, especially fish and seal, which contain large quantities of n-3 fatty acids, namely eicosapentanoic acid, EPA, and docosahexaenoic acid, DHA. EPA and DHA are found in fish, shellfish and sea mammals, and are very low in quantity or absent in land animals and plants.

Since then, there has been remarkable concurrence and congruence about the importance of n-3 fatty acids, as indicted by several thousands of papers that have appeared in the literature.

[Slide]

There is little doubt that n-3 fatty acids have a decisive importance in human nutrition. These fatty acids, particularly EPA and DHA, are present in human diets largely as fish. N-3 fatty acids are essential fatty acids necessary from conception through pregnancy, infancy and undoubtedly throughout life. A major reason for considering the need to maintain adequate intake of fish in

the diet is the important role of the n-3 fatty acid family in the prevention and modulation of certain diseases.

[Slide]

A partial listing can be seen in the table on the this slide. I apologize, it came out a little crooked.

The rest of the review provided by Dr. Connor we focus on the first two disorders because they are two of the most studied areas and form the most compelling body of evidence that fish consumption, with its requisite n-3 intake, benefits consumers from birth throughout adulthood.

[Slide]

There are two critical periods in life for the acquisition of essential n-3 fatty acids, during fetal development and after birth until the biochemical development of the brain and retina is completed. DHA is an important constituent of membrane phospholipids of these neural structures.

A typical example is phosphatidyl ethanolamine which is especially rich in the brain and retina. The specific findings of n-3 fatty acid deficiency are manifested in both the blood and the tissue chemistry. One note is a strikingly low concentration of DHA which may fall to as much as one-fifth or the normal amount in blood and tissues. In addition, the body attempts to replace the deficiency with another high polyunsaturated fatty acid of

the n-6 series that does not function as well Alzheimer's disease DHA. That would be in a diet deficient in DHA that we are referring to.

In the rhesus monkey an n-3 deficient diet, administered to a pregnant animal and then continued after birth, induces profound functional changes such as reduced vision, abnormalities of the electroretinogram, impaired visual evoked potential, more stereotypic behavior and perhaps disturbances of cognition.

Some of these findings have also occurred in human infants fed diets deficient in n-3 fatty acids, particularly those based on corn oil and coconut oil.

Although the experimental protocols in human studies have been less rigorous because of ethical considerations, in most studies of premature infants there have been visual impairment and abnormal electroretinograms unless the formulas contain DHA. A recent study of full-term infants comparing a standard infant formula with human milk and formulas enriched with DHA provided unequivocal evidence of considerable differences in visual evoked potential.

In all of the human infant studies the biochemical evidence in plasma, red blood cells and occasionally in tissues from autopsied infants have substantiated the n-3 fatty acid deficiency state.

[Slide]

Infants fed formula without DHA have lower concentrations of DHA in the brain than infants that were fed human milk which contained DHA. They also have lower intelligence.

[Slide]

During pregnancy the maternal stores of n-3 fatty acids and the dietary intakes of n-3 fatty acids by the pregnant women are of importance both in ensuring that the fetus has adequate amounts of n-3 fatty acids at the time of birth. All polyunsaturated fatty acids, including DHA, are transferred from the mother across the placenta into the fetal blood. Several studies in monkeys have indicated that when the maternal diet is deficient in n-3 fatty acids, the infant at birth is, likewise, deficient in n-3 fatty acids.

In humans, a recent study demonstrated that the administration of fish oil or sardines to pregnant women led to high levels of DHA in both maternal plasma and red blood cells, and in the fetal cord blood plasma and red blood cells at time of birth.

Several associational studies have indicated the importance of n-3 fatty acids from fish to the pregnant state itself and the delivery of a healthy infant.

Premature infants clearly have a higher mortality than full-term infants.

[Slide]

In the Scandinavian countries, women who eat a higher consumption of EPA and DHA from fish and seafood have a lower incidence of preterm labor, and deliver larger babies with an increased survival capacity.

In another study from Scandinavia, seafood consumption during pregnancy was associated with a reduction in postpartum depressive symptoms in women.

There are also several studies showing that n-3 fatty acids from fish may ameliorate the symptoms of attention deficit disorder, though long-term clinical trials have yet to be conducted.

[Slide]

Turning to cardiovascular effects, the strongest scientific evidence relates to the inverse relationship between the amount of n-3 fatty acids in the diet and in the blood and tissues and the occurrence of coronary heart disease and its many complications. The effects of n-3 fatty acids on coronary heart disease are based upon hundreds of experiments in animals, humans, tissue culture studies and even clinical trials.

While saturated fat and cholesterol in a diet are pathogenic for coronary heart disease, the n-3 fatty acids

from fish are actually protective and, by a variety of mechanisms, prevent coronary deaths and, in particular, cardiac arrest or sudden death.

[Slide]

In this table you can see a number of actions by which n-3 acts to prevent coronary disease.

[Slide]

Some 100,000 Americans each year die suddenly from cardiac arrhythmias. Many are previously well individuals. This is a tremendous public health problem. There is strong evidence that n-3 fatty acids from fish can prevent sudden death. EPA and DHA have a strong anti-arrhythmic action on the heart. In experimental animals and tissue culture systems EPA and DHA prevent the development of ventricular tachycardia and ventricular fibrillation.

Even total mortality has been improved in several studies in which n-3 fatty acids from fish intake was high. Those men in the Seattle study who consumed salmon at least once a week had a 70 percent less likelihood of sudden death. They had high levels of EPA and DHA in their blood.

In another study by Burr and Wales, overall mortality was decreased by 29 percent in men with overt cardiovascular disease who were given n-3 fatty acids from

either fish or fish oil. This is probably by the reduction in cardiac arrest.

[Slide]

A most recent study about fish consumption and the risk of sudden cardiac death was from the Physicians Health Study in the U.S., in which 20,551 male physicians participated. The consumption of at least one fish meal per week was associated with a 51 percent lower risk of sudden death compared with minimal fish consumption. The total mortality in this example was also reduced by those who ate fish.

[Slide]

The Nurses Health Study examined the association between fish and n-3 fatty acid intake and the risk of coronary heart disease in a sampling of 84,688 women. Both fish intake and n-3 fatty acid intake were associated with a lower risk of coronary heart disease.

It is of interest that both men and women in these two massive studies derived great benefit from fish consumption. Besides benefits for coronary patients, the Nurses Health Study also showed that fish consumption was positively associated with fewer thrombotic strokes. Women who ate fish two or more times per week had greater than 50 percent reduction in strokes.

These studies provide support for dietary advice such as that of the American Heart Association which recommends that Americans consume two fish meals a week to maintain a healthy lifestyle. The pronounce effect of fish oil on hyperlipidemia is especially well documented and is supported by precise dietary studies in a diet rich in salmon oil. Fish oil especially lowers plasma cholesterol and triglyceride concentrations.

DR. MILLER: Mr. Collette, five more minutes.

MR. COLLETTE: Thank you. Pronounced postprandial lipemia occurs after the absorption of fatty meals with a high fat content. Pretreatment with fish oil greatly lessens the postprandial lipemia and this effect should be considered both anti-atherogenic and antithrombotic.

[Slide]

This would be the summarization of Dr. Connor's review. In summary, the evidence is now very strong that the n-3 fatty acids are essential for human development in the fetus and infant, and are likely to have a role throughout life. The antiarrhythmic effect of n-3 fatty acids is a discovery that has great relevance to the prevention of sudden death from ventricular fibrillation.

Fish consumption in this country and in the world has a profound effect for improving health and preventing

disease, as indicated by public health agencies such as the American Heart Association.

[Slide]

That basically is the presentation of Dr. Connor. I would like to conclude with some NFI comments. First, fish and seafood provide a multitude of nutritional health benefits, especially as a unique source of essential n-3 fatty acids.

Public health organizations, such as AHA and ADA, have concluded that n-3 intake is low in general and fish consumption should be two meals a week or more to derive the benefits associated with n-3's.

[Slide]

Health benefits from fish could be lost or diminished with an expansion of the national fish consumption advisory. If the restrictions are too extensive and/or if the consumer message becomes too alarming or too confusing to fish consumers, although we cannot be sure how all consumers would respond to yet another FDA advisory, there are signs that even the experts are confused. A doctor on the "Today" program in July of 2000 regarding the health effects of mercury on pregnant women concluded, "I say eat quiche." But, seriously, the prudent step right now is probably to limit fish consumption until we can be assured by both the EPA and FDA

that this wonderful and tasty source of protein and other nutrients is safe.

What was the take-away message? "Eat quiche instead of fish?" Limit fish? What fish? All fish? An EPA fact sheet on mercury and fish advisories notes that the RfD is not a bright line between safety and toxicity. NHANES data suggests that 92 percent of sensitive women are below the RfD.

According to Clewell's presentation yesterday and his analysis, there are less than one-half of one percent of those in the NHANES who are above ATSDR's MRL and none are at the PMDA level.

Consideration must be given to the negative impacts of pursuing zero risk in terms of RfD through increasingly complicated and extensive advisories. At what point do fish just become too scary to eat? Expanded warnings could come at the cost of reduced fish consumption for many consumers, including some pregnant women who will lose the beneficial effects of n-3 fatty acids.

If you put a warning label on canned tuna, how many women will purchase it? Not everyone can afford more expensive fish and some do not like to prepare it. What will be their substitute for their n-3 sources? Will it be canned salmon or canned sardines? Not for many folks because most U.S. consumers like bland fish.

There are also some suggestions of species that I have seen throughout the presentation. I would just like to also mention that we need to be cautious when we recommend substitutions. Many of the fish listed, like bluefish and herring, also fall into the category of fish--it is like salmon, you have people who eat those fish and then you have other people who would never eat those fish because they are not bland. Then, some of the species also that were mentioned are under strict fisheries management controls.

DR. MILLER: Can you come to a summary please?

MR. COLLETTE: Okay. Essentially then, the reality is that in reviewing the advisory the committee, and ultimately FDA, must carefully weigh all of the information available and consider all the impacts on the consumer health, both positive and negative. Thank you.

Questions of Clarification

DR. MILLER: Questions or comments? Dr. Hotchkiss?

DR. HOTCHKISS: Maybe you can help me understand this. I don't think there is a lot of debate about the positive health benefits of seafood, but it seems to me most of those benefits accrue to a different population than the one that is of greatest concern for methylmercury, in other words, more adult populations. Maybe you answered

this, but would your organization then support a two-tiered approach in which those populations that would likely benefit from fish consumption are encouraged to eat more fish, but that population which may be at greater risk, during pregnancy particularly and young children, would be discouraged from eating fish? Do you see those as mutually exclusive?

MR. COLLETTE: I am not sure and maybe Dr. Connor may want to actually comment on the protective effects of n-3 and how that relates to your question. There is a growing body of science though that does relate to the importance of n-3 in fetal development. It is an area that started after a lot of the cardiovascular research but it is an emerging area of scientific exploration, and it does seem that there are some pretty compelling studies that are coming out showing that there is a benefit to the pregnant mom and her developing fetus.

With respect to a level for children, it seems to me that the NHANES data, if I recall, showed that they were essentially I think all under the RfD. I guess the bottom line answer really is that I think the consumer message has to be pretty straightforward, and I think having two messages out there would be rather confusing. I think it would need some real serious study in terms of what kind of impact it would have.

DR. HOTCHKISS: As I recall, there are something like 16 states that have a two-tiered message out there. It seems to me there is some experience with this kind of message. I noticed that you didn't talk much in your review of positive health benefits about that to the fetus and so forth. So, I am a little confused about your answer. You are saying that we don't know enough about the positive health benefits; that we should recommend low consumption for this population and high consumption for another population.

MR. COLLETTE: No, I guess the point of my answer was that it seems to me that both populations can benefit from the n-3. I don't think we would want to discount the utility to the other population you are speaking of.

I guess the other point too is that I think that the FDA advisory is really designed for that sensitive population you are referring to. So, the one advice that does exist is designed to address that particular group the greatest.

DR. MILLER: Dr. Aposhian?

DR. APOSHIAN: This is a difficult talk to respond to because the first part has some very good science and the second is obviously commercially related. Dr. Connor, can you hear us?

DR. CONNOR: I can hear you if you speak loudly.

DR. APOSHIAN: All right, I will try to speak loudly. Let me first of all say I admire your work; I am very much aware of it and I congratulate you on your accomplishments.

I was just wondering though about the Framingham Study, the nurse study, the men's study. Fish intake says nothing about the mercury content of the fish that people were eating in that study. I am very curious, and we appreciate your comments about the study in Finland which more or less suggests, and members of our committee have these papers which were handed out just a little while ago, that mercury even in subtoxic amounts is a risk factor for coronary and fatal cardiovascular disease, and that is based on the Finnish studies. Do you have any comments about the Finnish studies?

DR. CONNOR: I don't know the Finnish study. I have before me a study by Kales and Goldman which came from Harvard School of Public Health and the Children's Hospital in Boston. Obviously, the problem of mercury and contamination of the oceans is a real one. I think we have to weigh the benefits versus the benefits of excluding fish from the diet or advising people not to eat fish against the very positive health benefits which I think pertain throughout life.

There is one consideration for infants I think. The infant formulas now have DHA and arachidonic acid added to them. These are available in the U.S. and probably will be used by more and more mothers. So, this takes away the need for infants to eat fish that might be contaminated by mercury. I think the danger of mercury to the central nervous system is obviously more during the time of development than later in life.

I don't, myself, see hazards from mercury in the limits that we are ingesting them for adults that are susceptible for coronary heart disease.

The other question pertains to the habits of life. Certainly, if people have never eaten fish because they thought it was toxic for them and then they are encouraged by their doctors to eat fish at age 50, they might have difficulty. So, the habitual diet is of some importance too. I don't know if that answers your question.

DR. APOSHIAN: Yes and no. I will be certain copies from my office are sent to you. You might be interested in these papers from Finland because during the NRC meetings the papers were debated and finally some comments were made about that as far as the importance of the amount of mercury in the fish and the incidence of

cardiovascular disease in the Finnish men population, not the younger people. I appreciate your comments very much.

If I can now address a couple of comments to Mr. Collette please, I think one of the major problems is the ignorance of the American people. And, I think that if an educational program was put forth by the FDA or by the fish industry or a combination of people that one could call impartial, I think it would be a great help to educate people, especially pregnant women and women of childbearing age, as to the benefits of fish and the problems with certain kind of fish. I don't think anyone on this committee would want to see pregnant women not eat fish. I would be surprised if anyone wanted that.

But I think the problem is, and perhaps the fishing industry does not realize this, the problem is that pregnant women and women of childbearing age have to be informed and educated. So far, neither the FDA is doing that nor is the fish industry doing that. No one wants to put the fish industry out of business. Everyone would like to see everyone improve their economic status, but I don't think it is unreasonable, if the fishing industry does not want to pay for it, to ask Congress for a pork pie allocation to set up an educational program for the American woman that is going to be pregnant.

I spend a month a year near a fishing population, the oldest fishing village in the United States, and no one questions the desire or the wish of the working fishermen. They have no desire to hurt people. There should be some kind of an educational program. In the many years that I have been around, I have never seen anyone in the fishing industry try to support such a program, impartial program. There is no question about Dr. Connor's work. It is first-class work. It is about the fatty acids. But it does not take into consideration for us right now the amount of mercury in fish. No one says you should not eat fish; the question is which fish should we eat or how much of certain fish we should eat. I wish the industry would try to address that program in the future.

MR. COLLETTE: Thank you for that comment. It is interesting, we have trouble raising money in our industry just to market our product. So, the resources to do that are certainly an issue.

I would like to point out again though that we do have an educational area on our web site. We do have information about mercury. There is a direct link to the FDA advisory. So, with our web site we have tried to provide some information.

I would also like to point out that in the packet that you received yesterday there is a group called

International Food Information Council, and they have done a balanced piece on fish that is in that packet. In it they do talk about the benefits of fish and seafood, but they actually have the exact wording of the advisory, or very close to it, and I do believe they put this out as a peer reviewed piece of information before they published.

So, that is something that is out there. Our organization also has tried to help get this out to people. So, there are some materials out there and there are some efforts on education. But resources certainly are an issue.

DR. MILLER: Dr. Shannon?

DR. SHANNON: My questions were answered.

DR. MONTVILLE: I was just wondering if you have done any back of the envelope calculations on what percentage of the bad fish is actually eaten by women of childbearing age, and if a strong message went out on good fish/bad fish, that might not be more than offset by the encouragement to eat the good fish.

I also think this idea that people might stop eating fish because of this, if you look at the example of the alcohol advisories for pregnant women, it is certainly not true. Once they are done being pregnant they drink again. And, the alcohol industry is doing fine despite that warning.

MR. COLLETTE: The basic answer to your question is, no, we have done that kind of a calculation. I think it does get down to the part of the FDA message that maybe needs to be brought out more strongly, and that is that consumers should be eating a variety of fish. If you look at the top 20 most commonly consumed commercial fish species in the United States, and if you take sort of a weighted average of all those and then basically you take the data in the FDA data set and make a calculation, the weighted average of methylmercury there is actually quite low.

I guess what I am trying to say is that for most of the top commercial species that are sold in the United States, the ones that most people eat, upwards of 85 percent fall into that low category. So, that is where we need to get people to go, in my opinion, to point out the major commercial species and to say eat a variety of fish. It appears further down in the advisory. Maybe it needs to be brought up and be pronounced more but I think that may be one thing to consider.

DR. MILLER: Dr. Nordgren?

DR. NORDGREN: I am addressing this to both of you, and I am concerned--

DR. MILLER: Could you speak directly into the mike?

DR. NORDGREN: Yes. The essential fatty acids, and the question I have is are these essential fatty acids necessary as a dose, or is it like a vitamin? You need some and that is enough, and you don't need tons of it? Have these studies addressed this issue?

MR. COLLETTE: I hope Dr. Connor heard the question.

DR. CONNOR: I didn't quite hear the question. Bob, perhaps you could repeat it for me.

MR. COLLETTE: Well, I think the question essentially was, in the various studies that were reviewed in your paper, did the studies examine sort of a dose response? Is that how you put it?

DR. NORDGREN: Yes, are these essential fatty acids necessary as a minimal amount or is more better? Is there any evidence one way of another along those lines? Any good scientific evidence that the more you get into your system the smarter you are going to be?

MR. COLLETTE: Did you hear that?

DR. CONNOR: Yes, I heard the question. Those studies have been done in human infants by various investigators and I think the amounts that infant formula manufacturers are now putting into the formulas, Mead Johnson and Abbott Ross Laboratories, are probably in the middle range to have both safety and enough of these fatty

acids. For example, two-tenths to three-tenths to four-tenths of a percent of total fatty acid as DHA is being added by the infant formula manufacturers. We do not know if more than that would be better. We do know that throughout the world human breast milk differs greatly in the DHA content. In the developing world and in China DHA may be as high as one percent. In the U.S. it is about two-tenths of a percent or lower, probably because of the influence of the diet of the lactating woman. So, I hope that that answers your question. I think we have tried to stay in the middle ground in the recommendations. The World Health Association has made similar recommendations about the content that needs to be present in infant formulas to simulate as much possible human milk.

DR. DWYER: Isn't it true that the soon to be released micronutrient report of the National Academy of Sciences will cover fat and fatty acids? I believe you, Dr. Miller and also Dr. Russell, maybe others, were on those panels.

DR. CONNOR: I could answer that to some extent. I think a number of people have communicated with the Food and Nutrition Board, National Academy Sciences report. As far as I know the one on essential fatty acids is still being compiled. So, that isn't out yet but I would agree with you that that would be of great help in establishing

certain standards of adequacy. But I sort of summarized for you the literature as I have been able to understand it.

DR. MILLER: Other comments or questions? If not, thank you very much.

MR. COLLETTE: I would like to thank the committee, especially so late in the day, for your attention.

DR. MILLER: Knowing how anxious we all are to get away from the table, I am going to beg your indulgence for a couple more minutes for some discussion about what is going to happen tomorrow.

In the first place, we have a limitation on time because a number of you have to make planes out of Reagan and out of BWI and get there early enough to get through security, and so on. The secretariat has arranged for shuttles to take you to the airport. In order for this to really work, we have to try to be done by about 3:30 or it is going to make things very tight.

What we are going to do tomorrow in order to facilitate this is after the remarks made by members of CFSAN, we will go into a session to try to look at three major areas that should be able to support our--what is being distributed, by the way, are FDA statements for tomorrow.

Anyway, there are three areas, toxicology, consumption and risk communication and I have asked three of our colleagues to lead those discussions, Dr. Fischer for toxicology; Dr. Dwyer for the consumption data; and Dr. Scherer for the risk communication. Hopefully, we will have 20 or 25 minutes for that. Following that, I will then operate in the following way: We have five questions that we have to respond to and, rather than trying to gain a consensus directly of the committee, I will poll each member of the committee separately and ask for your remarks on the question that is being asked of us, and do that for all five. Hopefully, we can get all of your remarks on this and try to develop some kind of a sense of what the committee's feelings are and provide a record of what each individual committee member's responses to the questions. These will be transcribed and can be made available to the committee. The entire transcript of the entire three days will be on the FDA web site and can be obtained there. But our discussions will be made available to each member of the committee.

The agency then will take this advice from the members of this committee and will generate a course of action based on our recommendations. So, hopefully, by doing it that way we can get done in time for people not to miss their airplanes. So, think about it tonight and we

will begin tomorrow morning at 8:30 as usual, on the dot, assuming we can get through the traffic.

[Whereupon, at 4:30 p.m. the proceedings were adjourned, to resume on Thursday, July 25, 2002 at 8:30 a.m.]

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