internally from industry and from other governments about factors that may lead to economically-motivated adulteration. And we seek, for example, products for which compensation is based on characteristics determined by non-specific tests. For example, of protein levels. The melamine, we think illustrates that. Well, they were actually testing nitrogen. So that's an example. The question is, what other examples are there of tests that are like that?

We also are looking for information where there's dramatic shifts in supply. If suddenly the supply of a product shifts to a new region, a new set of companies, a new country, in a very dramatic way, because perhaps the price there is really low and maybe there is a too-good-to-be-true element that merits a further review. And we're initiating a survey of analytical tests in the food industry for measures of quality that could be evaded.

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This is our current thinking on this. We're not very far along in implementing this, but we figured we'd be remiss if we didn't implement these measures in anticipating the next possible case of economically-motivated adulteration.

So, in conclusion, forecasting economically-motivated adulteration is hard. This is a problem that was solved, that was recognized. It existed in the United States more than 100 years ago. It was addressed by Congress. FDA was largely created in part to remedy it, and we think we were fairly successful at that historically throughout most of the 20th century. But the most recent change of globalization suggest that it needs new attention, and in that sense, we wanted to share with you ideas on how to approach this now.

Let me just offer, by way of quick summary -- What you heard from Dr. Sundlof, in essence was what we've done with respect to

the particular case of melamine. I would characterize that as rapid response and really good scientific sleuthing.

And then what you have hear from me is our collective thinking about what we should do more systematically, not only to control melamine per se, and the threats that it poses, but really also to address the broader problem that melamine symbolizes. Thank you.

Q AND A AND DISCUSSION:

DR. MCNEIL: Well, thank you, Randy and Steve. Are there questions? These presentations were all so fascinating. Yes, Larry?

DR. SASICH: Thanks very much for the presentations. I actually have two questions, and I think it's a very good idea to move forward and survey analytical techniques that might not be very specific.

I think you mentioned foods, but I was thinking of pharmaceutical agents also.

And when the New York Times first started running stories about the heparin -- the heparin being a porcine source -- the first thing that came into my mind was thyroid. "Desiccated Thyroid," I think, is still marketed in this country and it's a porcine source. And if I'm not mistaken, the assay for thyroid hormone is still iodine content. And so that was my conspiracy theory.

The second thing is, is the agency looking at bio-engineered drugs and how un-regulated or counterfeited or however you might want to put it, may be coming into the country?

The reason I raise this question is that there were press reports, again, human growth hormone being smuggled into the United States by compounding pharmacists and re-sold in the anti-aging industry. What kinds of risks would back-room bio-engineered pharmaceuticals pose to the American public?

Here, you know, the economic

equation kind of changes a little bit. It's not so much in terms of volume, but just the cost of the product is so high, and can you significantly reduce your cost of production by bringing a product in from a back-room in China into the US? Thanks.

DR. MCNEIL: Would you like to comment on that?

DR. THROCKMORTON: Yes. I'll comment on the last one. I don't know much about desiccated thyroids, so --

As regards the risks of products coming from outside the country that are counterfeited or smuggled in or something like that, that is something that we've talked about and thought about a great deal.

One particular place we talked about was as a part of the agreements that we recently reached with China and the Chinese FDA and some of the things that we're going to be working with them on to improve the quality of products in both of the countries. We sat

about looking at the kinds of risks -- Where might risks occur for products manufactured in China either legally or otherwise that might get into the country? And you pointed out one very good risk -- a very highly profitable product that might be produced, counterfeited, and then used in ways in other than we'd like to. And so as a part of that agreement, we were asked to identify a group of products that we wanted to work in particular with the Chinese arm to help understand how they were manufactured, where they were being manufactured, and things.

And this group of products -- I don't remember if growth hormone was the specific product we named, but a group of products like this -- Where highly profitable, relatively easy to engineer, you know, that kind of a product we asked for specific conversations with the Chinese that we've been having, and so that is one kind of a risk that we did identify.

Others that you can think about are relatively inexpensive products to produce that are used widely in this country -- products that obviously have an illicit potential for use and that otherwise would be dangerous, at very low quantities. Those are the kinds of risks that we identified and have been discussing with the Chinese.

DR. MCNEIL: Frank, Did you want to comment that?

DR. TORTI: Just to add to what Doug said, I mean, the intent of putting together, and really the message for you, a group of scientists and a group of economists from Randy's group and members of each of the centers in a group to tackle this, is that these are in fact very complicated issues that touch on so many areas that -- Sort of bringing the science community, the community of economists, and groups who think about this from other aspects as well into one group that's continuously sort of filtering through

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this information and Larry looking for things, I think, very interesting suggestions of desiccated thyroid and its assay. To just sort of tee up and then explore is the way we're going to have to approach this, so I think really science can be brought to bear on this.

DR. PARKINSON: Just -- I congratulate the pro-active, the anticipatory thinking. But when I looked at your list of things, one thing you might want to add, real world being what it is, is to make it really easy for people to report what they suspect might be going on.

I don't know -- whether that's a web -- I don't know how I would do it. For example, if I realized that the desiccated thyroid I was taking was not -- That's for you, Doug -- was not pure. How do I report it?

So, that's -- I just made that comment because I think the reality is you're more likely to learn about these things from

people who are concerned about it, who've heard about it, from gossip about it, rumors -- Even, now that you have international offices, that will probably even be more effective -- Not that pro-active anticipatory thinking based on economics is not valuable.

DR. LUTTER: We're here to solicit good suggestions, and that's one that we welcome and will contemplate how to do it effectively and have an answer for you at the next meeting, so thank you.

DR. PARKINSON: "Human intel" I think is what they call it, right?

DR. MCNEIL: Erik?

DR. HEWLETT: I have a question for Dr. Sundlof about the dilution factor of the melamine getting into the human food supply.

You mentioned that the dilution factor reached a point where you would need to eat a huge amount of meat. Was that the natural, intrinsic dilution that occurs with the processing of the product, or was that

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predicated on there being dilution of the contaminated meat with known un-contaminated meat?

DR. SUNDLOF: No, that was the meat of an animal that was -- We made some assumptions about how much melamine an animal -- a pig or a chicken -- would actually ingest and we based it on that individual animal, not co-mingling meat from other animals.

DR. HEWLETT: Thank you.

DR. MCNEIL: Yes, Lonnie?

DR. KING: I have a question about authority here. So, these are intentional alterations and they have triggered your authority, but they are still intentional.

At what point do other agencies -- Homeland Security, et cetera -- come in and you know, what's the trigger point for this to be a terrorist act? Whether this was economically-motivated, it also had health outcomes versus something that's strictly a public health opportunity?

DR. SUNDLOF: Yes, well. Good question. During the first melamine and the second melamine -- During the first melamine, we had conference calls, daily conference calls, that included not only HHS -- We had CDC and the Secretary=s office. We had Homeland Security. We had State Department. We had EPA. We had some of the trade agencies that were very concerned about that.

So, there was a lot of interest from a lot of different people. FDA also has an Office of Criminal Investigation and Criminal Investigation was involved. It ended up in the prosecution of the company that was importing the wheat gluten from China because it turns out they knew that they were importing products that were adulterated. So yes, a lot of people were involved in that. And Homeland Security has also been very much involved in this more recent melamine situation too -- trying to determine if there is some kind of terrorist plot associated.

DR. MCNEIL: I'd like to ask one of you a question. I don't know which one. You mentioned the need to look for early changes in the distribution of origin of products as a way -- of the supply chain -- as a way of potentially identifying cheaper products that hence, might have been contaminated.

Is it possible or do you already have a database that says for the biggest drug, say, or the largest percentage -- The drugs that are imported the largest -- The distribution of their current sources? Is that possible to do or is it changing so rapidly that you could never make a map like that to notice changes?

DR. SUNDLOF: I think I'm going to see if Doug has a --

DR. MCNEIL: All right. Doug, it's for you.

DR. THROCKMORTON: In some senses it probably depends on the kinds of drugs you're talking about. So, for some drugs for

prescription products, my guess is that we have a fair amount of that information. There's some products, however, where we don't routinely obtain that information from the non-prescription drugs in particular and things where changes in sources for materials be happening fairly frequently.

DR. MCNEIL: But do you have some sense of which of those non-prescription drugs are imported in the high enough quantity that they would be worrisome? They don't care about little things.

DR. THROCKMORTON: I think to step back from that, sort of if you generalize that comment, it goes back to the sort of risk assessment --

It's not just a matter of who is changing sources for their materials frequently, but does that present a risk? Is there a credible way that that could cause harm that could be -- That's the piece you have to include in all of that. I mean, I

agree that's one factor but there's also steps in place that are going to prevent anything like that from leading to a, you know, a potential problem. That's why Randy's point is it's a very complex thing. You have to sort of factor all of those things in.

DR. MCNEIL: Just if I could follow up with one more, just taking Larry's comment about the desiccated thyroid for example, would you know now where that is coming from since it is a prescription drug? It's not that expensive so it might not be....

DR. THROCKMORTON: I'd have to first check and see if it is actually a prescription drug. I don't know whether it is or it isn't or whether it's something that's obtained.

DR. MCNEIL: I think it is. I think it is.

DR. SASICH: Yes. It's amongst the top 200 most frequently prescribed drugs in the US in 2007. I don't know where the source

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of the thyroid glands is, but it's just one of those things where here is a natural product that has a very insensitive assay and it seems like it would be very easy to contaminate it, and I don't know if the contaminant might be a risk to public health.

DR. THROCKMORTON: It seems like a good one for us to look into.

DR. LINEHAN: Well, this is sort of a consumer question. I guess I was thinking about the ease of reporting, and it seems like we hear around the table here the New York Times reports on things and then we know that they exist at least as consumers.

A couple of years ago there was this series of articles about salmon -- whether or not it was farm-raised or wild, and what was healthier and what wasn't healthier, but, I guess, one of the questions is that some of the salmon were adulterated in the sense that they were fed a dye or something to make them look pinker. Now how does that fit

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into the framework of reporting and so forth?

DR. SUNDLOF: One of the -- in fact, just last week I had a conversation with the National Fisheries Institute, and this has been a perennial problem with seafood. Not so much the fact that there was -- salmon was fed canthaxanthin which gives it the pink color. That's an approved feed additive. They are supposed to list it on the labeling though, and if they don't then they are in violation, and so we can take regulatory action against them.

Seafood industry -- there's a number of things, adult fraud, economic fraud-wise that go on. One of them is substitution so you think you're getting grouper but you're really getting tilapia, a much cheaper fish. This happens apparently quite a bit, and the National Fisheries Institute is very concerned about this.

There's other things that add weight to the product because product is sold

on a weight basis. So, something called glazing in which they actually spray water on it and they freeze it for transport, can add weight to the product so you're not getting as much as you think you're getting when you're buying on a weight basis.

So there are a number of those issues, I think. We're concerned about economic fraud, but we're really concerned about economic fraud where it also presents a public health risk. So, with our resources being limited, we try and focus on those areas that really represent more of a public health risk. And we're hearing from our industries that we need to be spending a little bit more time -- The whole broken window theory of law enforcement is that you don't fix the window. Once it's broken, it will proliferate and so that is something I think we really need to keep in mind as we go forward.

DR. MCNEIL: I think we have time for one more quick, very quick, question.

Rhona. Very quick and quick answer. Turn on your mike please.

DR. APPLEBAUM: We've already alluded to the fact that you're all working together because you know if you go back to 9/11, there are things that are being identified -- whether it's sector vulnerabilities, so there's obviously models there as relates to what's been done in counterfeiting -- whether you're looking at pharmaceuticals or whether you're looking at foods, what was done with terrorism.

But, I was just wondering, and again, just to put this on the table and get back to us, we talked about back in 2001 the need for ISACs, information sharing and analysis centers, to make sure that you can help gauge what is going on. So, for example -- and there's a lot of history in the food industry. I think its adulteration is like the second oldest profession anywhere. But if you look at things from an economic perspective,

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and that's where Randy has had to focus, as it relates to when you see bio-fuels -- when you see sugars, you see corn being switched to a fuel area, you know that some point in time the need for bricks and juice, bricks and various beverages and food have the potential.

So you adjust it again with everybody being as busy as they are, being on the ground, fighting the fires as opposed to being 30,000 feet to see what can be done from an ISAC perspective,

I encourage FDA to look at that even more closely because sometimes there's hints. You hope it's going to be -- you can get ahead of the power curve. But sometimes you can see certain things in terms of where the economy is going and where the little rascals want to go in terms of making the next buck.

DR. MCNEIL: Okay, I think we are nearing the end of this morning's session. I'd like to thank you all for participating, thank

our guests as well for listening. We will now break until 1:00.

We have a very busy agenda. The public session will start promptly at 1:00, even if I am the only one here. So, and I wonder if the Science Board can just meet briefly up here for a few minutes before we break for lunch.

(Whereupon, the above-entitled matter went off the record at 12:04 p.m. and resumed at 1:03 p.m.)

OPEN PUBLIC HEARING:

DR. MCNEIL: Okay, I wonder if we can all get seated and start. I'd like to welcome you all to this afternoon session, which is going to be devoted to discussing the BPA Report that was prepared by a subcommittee of the science board.

Before doing that I would like to acknowledge that written comments were submitted to the board by several groups. The Environmental Working Group, Mrs. Rachel

Rawlins and the Breast Cancer Action Group, The National Resources Defense Council, The American Chemistry Council's Polycarbonate BPA Global Group, and Dr. David Epel from the Stanford University Hopkins Marine Station. The Board has all seen those comments as part of their preparatory materials for this meeting.

I would like to thank at this point and on behalf of all of the sub-committee the hard work that Dr. Martin Philbert and his committee did in reviewing the staff's document and in their part in reviewing lots of materials to supplement that document.

I'm particularly grateful that two members of the sub-committee are here. Antonia Calafat there, and John Vandenberg. I understand that Garret FitzGerald, who is currently at a site visit at Harvard, will be joining us by phone approximately at 2:00.

We have nine individuals who have

asked to make public comments. These are in addition to or separate from what has already been received in writing.

We have to have a very tight schedule here so what I am going to do is ask each individual to talk for three minutes, and there will be a time period of two minutes for the Science Board to direct questions to you. There will be a firm stop at five minutes, so if you go over your time then there will be no questions from the Science Board.

So I am hoping that you will be able to accommodate this schedule so that we can have adequate time for Dr. Philbert's presentation and discussion by the Science Board. So our first presenter is --

Sorry. I was just told I have to read a statement, so "Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure that such transparency at the open public hearing of the

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advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

"For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement," oral in this case, "to advise the committee of any financial relationship that you may have with the sponsors, their products, and if known, their competitors. For example, this financial information may include a sponsor's payment of your travel, lodging, or other expenses in conjunction with this meeting.

"Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address the issue of financial relationships at the beginning of your statement, it will not preclude you're your speaking however."

So with that, I would like to move

on and invite Dr. Olga Naidenko from the Environmental Working Group to make her statement.

DR. NAIDENKO: Good afternoon. I am a senior scientist with the Environmental Working Group, a non-profit advocacy organization here in Washington, D.C. I do not have any financial relationship to BPA producers of any kind.

I am very grateful for the opportunity to provide today our comments regarding the FDA's draft risk assessment for BPA in food packaging. We are very pleased with the vigor and the quality of the subcommittee report, and we fully support the determination that FDA cannot substantiate the safety of the current BPA uses.

FDA estimates of BPA intake for infants and adults are unacceptably close to the concentrations that show health effects in the low dose toxicity studies. This seriously undermines FDA's claims about the safety of

current BPA exposure, including exposures from canned liquid infant formula, canned foods, as well as polycarbonate baby bottles. As demonstrated by findings from hundreds of scientific studies published in peer reviewed literature, the margin of safety is simply non-existent.

Adopting the subcommittee's recommendations as written and publicly available on Wednesday, will address most of the concerns that EWG has raised in the comments which we provided to the science board on October 24. This concludes with the sub-committee, that included in the risk assessment the studies deemed adequate by the NTP, would call into question the safety of BPA exposures from food packaging.

Most alarmingly is the FDA has used outdated decade-old study of only fourteen samples of infant formula which were used to make safety assessments. We know that Canadian health authorities have used the same

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set of data as they came to a markedly different conclusion. They announced immediate action to reduce BPA exposures for infants. EWG testing of canned food, especially liquid infant formula indicated that infants are exposed to dangerously high levels of this chemical.

So, today we have reason to producers of infant formula, asking them to voluntarily repackage their food and eliminate BPA contamination. Formula makers can and should reduce BPA levels while safer packaging is investigated. And parents and pediatricians need to be informed about this, and they need to look for options that will protect the health of their children.

We know that early life exposure to BPA can alter the developing brain of infants, can pose serious consequences for the nervous and reproductive system, and we know that we only have one chance to get it right for every child that is born today, for the

four million of children that are estimated that will be born in the next year

We urge the Science Board to impress upon the FDA the need for immediate action to reduce BPA levels in food and in formula. Thank you very much for your attention today.

DR. MCNEIL: Are there any questions of our speaker? Okay, if not, then we'll move on. Thank you very much. We'll move on to Dr. Steven Hentges, from the Polycarbonate/BPA Global Group. Thank you for coming.

DR. HENTGES: Thank you. Good afternoon. Thank you for this opportunity to provide comments on the Bisphenol A subcommittee draft report. I'm Dr. Steven Hentges, and I represent the Polycarbonate/BPA Global Group of the American Chemistry Council.

The Science Board is receiving many diverse viewpoints on Bisphenol A. But

the common ground we all share is a commitment to do what's right to protect the health and safety of American consumers, adults and children alike.

For our part, we have sponsored extensive research and analysis for many years to understand Bisphenol A's potential for health or environmental effects. We have made our research publicly available, published it in peer review journals, and shared it with FDA and other regulatory agencies, and we will continue to do so.

The research we sponsor is conducted by respected scientists using accepted scientific methodologies, and we welcome scrutiny of those studies by any interested party. We have separately provided written comments on FDA's draft report on the safety of Bisphenol A and food contact applications. It's thorough, based on a sound analytical frame-work to review the most relevant data, and it's well-documented with

scientific support for its conclusions.

Importantly, FDA's assessment is consistent with the conclusions of other scientific and government bodies world-wide, such as the European Food Safety Authority, Health Canada, the European Union, and NSF International, all of which have completed or updated their assessments this year.

We rely on their conclusions, which are that polycarbonate plastic and epoxy resins are safe for use in food contact applications. We appreciate the sub-committee's work on this very important subject, and we note that the report provides many thoughtful recommendations that may help FDA to further improve the quality of its assessment.

It is then FDA's role to evaluate those recommendations, implement the ones it finds appropriate, and produce a scientifically sound and defensible assessment.

We also note that the sub-committee report reaches certain conclusions, apparently without adequate analysis. For example, the executive summary states, "Coupling together the available qualitative and quantitative information, Including application of uncertainty factors provides a sufficient scientific basis to conclude that the margins of safety defined by FDA as adequate are in fact, inadequate."

This definitive conclusion and other similar statements in the report do not appear to be based on a sound and thorough scientific analysis, and in particular, one that follows the sub-committee's own recommendations.

The sub-committee also concluded that FDA should "consider in its assessment, all studies judged by CERHR as adequate and of limited or high utility. We fully support FDA's consideration of all relevant scientific research in its assessment. If FDA then

identifies additional studies that are of sufficient quality for conducting a safety assessment, they should be considered and given appropriate scientific weight."

CERHR's weight of evidence evaluation, based on adequate studies of limited or high utility, itself concluded that there was only limited and inconclusive evidence that low doses of Bisphenol A could cause certain health effects.

We note that limited and inconclusive evidence cannot support the definitive conclusions stated in the sub-committee report. We agree with CERHR and FDA that additional research would help to improve our understanding of Bisphenol A's potential to cause health or environmental effects.

Like FDA, we are sponsoring additional research to address key scientific questions and uncertainties, and we look forward to making the results of the completed research available.

We encourage FDA to act promptly to complete its assessment after receiving your recommendations, and you have our assurance that the commitment to public health that we all share will remain our highest priority. Thank you.

DR. MCNEIL: Thank you. Are there questions? I would just comment right now that the last bullet to which you referred has been altered, and you will see that in the presentation of Dr. Philbert.

DR. HENTGES: Thank you.

DR. MCNEIL: But thank you. Okay, we'll move on to Mr. Ronald Weiss from his law offices. Mr. Weiss?

MR. MURAKAMI: Good afternoon. My name is Stephen Murakami. Robert couldn't be here. He had to leave.

I thank the sub-committee for an opportunity to address you this afternoon. And I'd like to inform you briefly of some of the legal activity that has developed as a result

of this very important public health issue.

On March 12, 2007, Robert Weiss and I filed the first civil law suit in the country against the manufacturers of the baby bottles and sippy cups for their misrepresentations, either intentional or negligent, and for their lack of disclosure that their products are made with a potentially toxic substance that may be causing harm to infants and children.

Since that time, fourteen months approximately, after we filed our case, there are now 35 cases, similar consumer class action cases filed throughout the United States. A multi-district litigation was formed and venued in Kansas City under the auspices of Judge Ortrie Smith who will consolidate all of the actions filed. And our first meeting will be held on November the 18th.

While I mean no disrespect to our well-intentioned panel members and I commend

you for your efforts and labors in this regard, I have to ask you on behalf of our clients and the rest of the American public, when is the FDA going to take decisive action?

Our clients and the public are confused by the seemingly inconsistent information that's coming from one branch of government or one agency and another. They are entitled to decisive action. We ask you to take all speed and ban Bisphenol A from baby bottles and sippy cups. Are we waiting for another DES debacle where generations of children are still getting cancer? I know we don't want that. I encourage you to please resolve this issue, on behalf of the public, as soon as possible. Thank you.

DR. MCNEIL: Thank you very much. Are there questions? Thank you. We will be taking a vote on this matter today for the Science Board.

MR. MURAKAMI: Thank you.

DR. MCNEIL: Okay. Dr. Diana

Zuckerman from the National Research Center for Women and Families?

DR. ZUCKERMAN: Thank you very much. I'm Dr. Diana Zuckerman, president of the National Research Center for Women and Families, and I have no conflicts of interest.

Our center scrutinizes medical and scientific research to see what is known and not known based on that research.

In addition to my current position, I am also a fellow at the University of Pennsylvania Center for Bio-Ethics. I was trained in epidemiology at Yale Medical School, worked at Harvard and Yale, and have worked for non-profit organizations and Congress on health policy issues since that time.

I strongly commend the sub-committee's report and we agree with the findings. I was especially pleased that you looked at the inadequacy of the samples of infant formula. I wanted to point out that in

addition to the fact that there were too few samples, they were also about 15 years old, so we don't really know how representative they are today. And also that all those infant formula samples that were in FDA's draft report were from the Washington, DC area so we don't really know how representative they are of samples from across the country.

They were too old, too limited, and too small of a sample, and we really need to know -- as the sub-committee pointed out -- the range of levels of BPA because the range is very broad, so it's not enough to look at the mean, and we agree with that strongly. We also agree with, really, all the findings of the report.

I think the big issue for us is -- We commend the sub-committee for saying that it's not enough to look at the levels of BPA in food containers because that is not the only source of exposure. So when you're thinking about safety regarding the food

containers, you do have to look at other sources of exposure, and so we were very pleased that the sub-committee mentioned that -- even though it's a much more complicated issue and we understand that.

I also wanted to mention that it's great to focus on children, but obviously you also need to focus on pregnant women, and that is more complicated because the foods and beverages consumed by pregnant women are going to be, of course, the foods and beverages consumed by almost all Americans. So, in addition to looking at children, let's look at those prenatal exposures.

And I guess the final point is that we are very pleased and we hope that the full Science Board will support the work of the sub-committee, but it still begs the question as to why the FDA's draft report was so inadequate, and why they rushed to judgment on the basis of such limited information, why they ignored so many excellent peer reviewed

studies in their analysis, and why they made so many fundamental flaws in their analysis ending up with an inadequate margin of safety.

And furthermore, why -- in response to the sub-committee report that was released this week -- the FDA parsed their words to suggest and to mislead the public into thinking that there is a general international consensus that BPA is safe?

It is true that the regulatory agencies, for the most part, have not banned BPA, but Canada did just put a ban on BPA in baby bottles. So, it concerns us that the FDA is continuing to represent the situation as if there is a consensus, as if we can reassure the American public that BPA levels are safe, when in fact, I think all the data suggests that there's a lot we don't know, but that the growing body of evidence is going in a different direction toward risks that are higher than we expected them to be.

Thank you very much.

DR. MCNEIL: Thank you very much for those thoughtful remarks. Are there any questions of Dr. Zuckerman?

Okay. And Jennifer Rogers from the Reproductive Health Technologies Project. Thank you.

MS. ROGERS: Good afternoon. I want to thank the FDA's Science Board for convening this meeting to review the draft assessment of BPA for use in food contact applications.

My name is Jennifer Rogers. I am the programs and policy director for the Reproductive Health Technologies Project. RHTP is a national non-profit advocacy organization. Our mission is to advance the ability of every women of every age to achieve full reproductive freedom with access to the safest and most effective and appropriate technologies for ensuring her health and controlling her fertility.

At RHTP, our work focuses on a Board range of national public health

policies, and we have often depended upon the scientific evidence provided by agency reports like the FDA's to help guide our programs and our policies.

RHTP does not accept any funding from for-profit companies, drug, or device manufacturers.

We urge the FDA to heed the advice of its independent scientific panel and consider all the evidence, as well as their margins of safety, especially considering the cumulative effects of BPA in not only food products, but from a multitude of human exposures.

RHTP provided comments at the last Science Board BPA meeting concerning FDA's critical regulatory role and BPA's use in plastic food containers, bottles, table-ware, and the plastic linings of canned foods.

RHTP was concerned the FDA draft report concluded that BPA was safe for use in these items based largely on two studies, both

of which were funded by industry, both of which used animal models which had been shown to be non-responsive to estrogen.

However, we applaud the scientific panel's efforts to carefully evaluate FDA's report. As you know, in the report, the panel criticized the FDA and concluded, "Similarly, to many organizations within and outside the women' health community, that the FDA's science was flawed."

Although the panel did not draw conclusions about the safety of BPA, we want to emphasize the growing body of evidence that indicates that this chemical is harmful, especially to the developing fetus, infant, and child -- even at low levels.

Numerous studies have found the far-reaching negative health impacts BPA has on women's and men's reproductive health and overall health, Including recent reports documenting that BPA interferes with chemotherapy and has even been associated with

high-risk of diabetes and heart disease.

As the Science Board considers what to do next, we encourage the FDA to review this report without political or private interest interference. We hope that the FDA will communicate with integrity their findings to the public, publish their work for independent scientific review, and disclose any censorship and/or conflicts of interest. We applaud the Science Board panel for its assessment.

Lastly, we urge the FDA to not ignore the scientific evidence in its formulation of public policy, especially when the health impacts on women, men, and children are profound. Thank you.

DR. MCNEIL: Thank you very much. Are there questions? Okay, then we'll move on to Dr. Sarah Janssen from the National Resources Defense Council. Is Dr. Janssen here?

Okay, then we'll move on to Mr.

Robert Rankin from the International Formula Council. Is he here?

MS. MOUNTFORD: Well, he's not here, but I'm here.

DR. MCNEIL: You're Dr. Janssen?

MS. MOUNTFORD: No.

DR. MCNEIL: Oh, fine. Okay. Tell us who you are.

MS. MOUNTFORD: Sure. My name is Marti Mountford, and I'm executive vice-president of the International Formula Council.

The IFC is an association of manufacturers and marketers of formulated nutrition products. For example, infant formulas and adult nutritional foods. Our members are predominantly based on North America. On behalf of IFC, I welcome the opportunity to comment on the recent report of the FDA Science Board.

The primary focus of the Council and its member companies is and always will

remain the health and welfare of infants and children around the world. Today, and in the days and weeks that follow, much will be discussed and debated about the science that is at the core of this issue.

I urge this organization and all who speak about the issue to put parents and babies first by clarifying the potential risks associated with BPA and providing appropriate and meaningful guidance. The infant formula industry takes all safety issues very seriously, and we support science-based efforts to continue to produce infant formula products of the highest-possible quality. When new information becomes available on substances like BPA, we support bringing that information forward through a sound regulatory process of scientific review and evaluation as the basis for regulations.

We support the thorough assessment approach currently utilized by the FDA and by numerous world-wide regulatory agencies. For

example, in Canada and Europe, and in Japan. None of these agencies has restricted BPA in packaged foods, but they've engaged in a thorough process of assessing any potential issues associated with BPA exposure.

This standard, multi-step evidence-based scientific process to establish a sound risk assessment is based on well-defined criteria. And we appreciate the sub-committee's important role in FDA's evaluation process regarding the safety of BPA.

We note that the FDA's draft assessment excluded many low-dose BPA studies because of their serious limitations, a decision based on a well-established review process for making regulatory decisions. There are may published studies that provide new scientific information about the mechanism of action of BPA, but are not designed for the purposes of assessing safety.

We are confident the Science Board will carefully consider the weight of evidence

and sound regulatory process, as well as conclusions of other regulatory agencies around the world as it evaluates the sub-committee's report.

As FDA noted on October 28, the present consensus among regulatory agencies in the US, Canada, Europe and Japan is that current levels of exposure to BPA through food packaging do not pose an imminent and immediate health risk to the general population, including infants and babies.

Further, all these agencies have concluded that trace amounts of BPA from food packaging are not a risk to human health. None of these have restricted BPA in packaged foods. Now, the IFC member companies continually evaluate food packaging and scientific research to guarantee product safety and quality. Our goal is to ensure the health and well-being of infants.

Because the questions about BPA have been raised, we have continued to work

with our suppliers to identify opportunities for packaging without BPA. There are no quick solutions though, and we would welcome solutions. But in the interest of safety and consumer confidence, any new alternatives have to be carefully assessed to assure the highest possible standards of quality. As soon as a safe and viable alternative is identified by the chemical and container industries --

DR. MCNEIL: Excuse me, one minute.

MS. MOUNTFORD: Thank you. We stand ready to bring these new containers to market as quickly as possible once they have been approved for use by the FDA.

Infant formula is the most highly regulated food in the world and remains the only safe and nutritious alternative for babies who are not breast fed.

As the FDA's press release, the October release, stated the Surgeon General Galson -- he said the most important thing parents can do for their babies is ensure they

receive adequate nutrition.

While the best source of nutrition for babies is mother's breast milk, infant formula remains the recommended alternative when breast milk is not an option. Additionally, Health Canada has stated the nutritional benefits of infant formula far outweigh the potential risks from BPA. On behalf of the council, I thank you for your time today.

DR. MCNEIL: Thank you, and thank you for being a substitute -- Are there any questions? Could we have the spelling of your last name for the record?

MS. MOUNTFORD: Sure. Mountford. M-O-U-N-T-F-O-R-D.

DR. MCNEIL: Thank you very much. Okay, we'll move on to Dr. John Rost, from the North American Metal Packaging Alliance. Dr. Rost?

DR. ROST: Good afternoon. My name is Dr. John Rost, and I am chair of the North

American Metal Packaging Alliance. I appreciate this opportunity to speak before the science board of the Food and Drug Administration. NAMPA and its member companies support sound science and trust the scientific review process that has protected our food supply for decades.

NAMPA appreciates and thanks the Science Board BPA sub-committee for its efforts. NAMPA urges the FDA to base its final safety assessment on a full and robust review of all relevant studies and their underlying data.

NAMPA believes that it is critically important for consumers of the United States to have confidence in the products that FDA reviews and allows for consumers to use and to facilitate this, the FDA must have access to appropriate information.

We fully support the sub-committee's recommendation that the FDA review

should include examination of the studies that the FDA originally rejected based on its determination that its studies were materially flawed.

We noted that the same studies were also rejected by reviews from the European Food Safety Authority. Additionally, the National Toxicology Program and the Center for the Evaluation of Risk in Human Reproduction Reviews, which included the analysis of these studies, did not yield conclusions dissimilar from FDA's draft assessment.

In all but one area, NTP rated the concern of BPA as minimal or negligible. The single area where the concern level was raised to some was based on insufficient evidence to lower that concern level and NTP called for more research which FDA has already proposed.

NAMPA encourages FDA to reexamine the studies as urged by the sub-committee. We believe this should be undertaken as quickly

and transparently as possible. We urge that FDA immediately call on the authors of the research in question to submit to FDA all information required for a full review, which would include all raw data and related information.

Additionally, all pertinent information to other experiments from the authors that may not have been included in the published reports should be requested. For example, the scientists who would be asked to submit data should also be asked if they attempted to replicate their data but were unable to do so, but failed to list that in their reports. Information required to be reported in relation to industry sponsored studies and on all research should be yielded at the same standards.

Additionally, all information should be submitted to FDA to allow it to determine if the quality of these studies meet the minimum requirements for consideration for

regulatory purposes.

Accordingly, NAMPA urges the Science Board -- its assessment to review the position taken by the sub-committee and the FDA, and also to consider the position on data assessment taken by other international regulatory bodies, including the European Food Safety Authority, Germany, Japan, Canada and the United Kingdom.

NAMPA is also aware of concerns that have been expressed about the integrity and independence of the subcommittee. Members in Congress and public interest groups alike, as recently as Tuesday of this week, called for the cancellation of this sub-committee report and today's meeting. Now that the sub-committee's recommendations have been made public, those same critics are now strangely quiet about concerns that the sub-committee's integrity and the independence of the process.

The process however, cannot be deemed legitimate only if it yields the

results desired by those who cried foul earlier this week. As a concerned stakeholder, NAMPA believes the public trust will be further eroded if all parties do not demand better. Thank you.

DR. MCNEIL: Thank you very much. Are there -- I just sent a note, and I don't know whether we know the answer about whether or not the FDA has the authority to do what you requested, in terms of asking authors of either private studies or -- you do have that authority?

Okay, I think the comment was just made that the FDA would welcome any of the raw data from any of the sources and we can talk offline about how to do that and what might be the next steps.

DR. ROST: Okay.

DR. MCNEIL: Thank you very much. Okay, Dr. Urvashi Rangan from Consumer Reports.

DR. RANGAN: Thank you. Good

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afternoon. My name is Urvashi Rangan. I am a senior scientist with Consumer's Union, the non-profit publisher of Consumer Reports.

We have no conflicts of interest, no vested interest in BPA manufacturing or use of it. We wish to thank the members of the scientific sub-committee for their report on the FDA draft risk assessment of BPA. We appreciate the level of depth of your analysis, your candor in your opinion and your careful consideration of public and scientific input. We applaud the report.

We also wish to thank the FDA at this time for providing this opportunity to make public comment. Today, the report that's been issued serves as yet another scientific consensus document that the FDA position that BPA is safe is wrong. As one reads through the answers to the many questions asked by FDA to the scientific subcommittee, it is clear that the FDA was mostly transparent in how its analysis was conducted and that's a good

thing.

However, the report underscores the severe limitations in the FDA analysis, including omission of hundreds of scientific studies and its assessment, shortcomings in the exposure analysis of BPA, limitations in the potential toxic endpoint range, that has led FDA to calculate an erroneous margin of safety. And this has been the basis of FDA's claim for BPA's safety in the marketplace.

Consumer's Union urges the FDA to stop their one-dimensional approach to assessing the safety of BPA, and to take this opportunity to analyze studies in concert, especially where cellular, animal, and human study observations are lined up with a common endpoint.

Consumer's Union is concerned that the FDA statement and their characterization of Canada's action to restrict the use of BPA that has been taken with an overabundance of caution, is cavalier and it is not rooted in

the totality of the current weight of scientific evidence.

The report today suggests that the FDA is not correct in its assessment of BPA safety, that it is inadequate, and that it is flawed. It is not clear why the FDA believes this move by the Canadian government is excessive. And while Canada often takes its cues from the United States, we applaud their efforts to protect their consumers from potential harm. It is not only right, but it is responsible, and the American public needs the FDA to follow suit.

We would like to offer the FDA a challenge to change their strategy on assessing BPA safety from a defensive one to an offensive, pro-active one. The American public is entrusting you to ensure that our marketplace is safe, and that chemicals like BPA are largely curtailed from wide-spread use, especially when consumers are currently ingesting amounts that approximate levels that

cause harm in animals.

We need you to account for the full range of possible BPA exposures, the full range of possible toxic endpoints, specific population susceptibility issues among others mentioned in the report.

In the meantime, in response to the Infant Formulation Council, there are alternatives for canned formula at this time. There are plastic bottles and there are readily alternatives available for the infant formula industry.

We also believe that the FDA should act responsibly, that they should ban the use of BPA in all food contact applications at this time so that consumers do not have to continue ingesting this questionable chemical while the FDA gets a better handle on the potential harm.

Consumer confidence in the plastics that they buy is in question and they need the FDA to step up to the plate and ban

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the use of this until we fully understand the wide range of effects. Thank you.

DR. MCNEIL: Thank you very much, Dr. Rangan. Are there comments or questions? Are there any other members of the audience who did not sign up to make a comment who would like to make a brief comment at this time? Emphasis on the brief.

Yes, please. Please identify yourself and any conflicts.

MR. COLANGELO: Good afternoon. My name is Aaron Colangelo. I'm an attorney at NRDC. We don't have any conflicts. Dr. Janssen with NRDC had signed up to speak, but was unable to attend. She's in California. I'm filling in for her.

I have three brief comments. First is that NRDC is happy with the sub-committee's report and we want the Board to adopt it in full. We recommend that the FDA re-do their analysis to address the serious criticisms and concerns itemized in the sub-committee's

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report.

Second, missing from the charge questions to the sub-committee was the question of whether BPA was safe as a food additive and whether it should be permitted to be used in food contact applications.

The draft report did not expressly address this question, although the statement in the report that the -- I'm sorry -- the sub-committee's report did not directly address this question, but the statement that the margin of safety is inadequate would suggest that the sub-committee has taken the position that it should not be approved as a food additive. We would have preferred had that been expressly asked of the sub-committee.

Finally, the governing legal standard should determine the outcome here, the outcome of the Board's review. Under the Federal Food, Drug, and Cosmetic Act, the FDA may not approve a food additive if it "fails

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to establish that the proposed use will be safe under approved conditions of use."

In other words, the statute establishes an affirmative obligation on the FDA to demonstrate safety before a food additive may be approved. The FDA's regulations repeat this and reiterate this burden of proof. The regulations state that a food additive may not be approved if "it has not been shown by adequate scientific data to be safe."

Therefore, under both the statute and the regulations, the burden of proof is dis-positive. The FDA must affirmatively establish safety before allowing BPA to remain on the market in food contact applications. Thank you.

DR. MCNEIL: Thank you very much. We're glad you were able to fill in.

MR. COLANGELO: Thank you.

HEARING REPORTER: Can you just re-state your name? Did you get that name?

DR. MCNEIL: No. Re-state your name.

MR. COLANGELO: Sure. My name is Aaron Colangelo. C-O-L-A-N-G-E-L-O. I'm an attorney with NRDC.

DR. MCNEIL: Okay. Great, thank you. Is there anybody else who would like to make a statement from the audience?

Are there any questions from the Science Board for any of the speakers who just presented their thoughts?

All right. What I'd like to do is --

DR. PENA: If there is information that people would like to submit to the agency -- data supporting any claims or assertions, they can be submitted as written comments and I would encourage you to contact me. My e-mail address and number is outside. We would welcome those comments to the agency.

REPORT FROM THE SCIENCE BOARD

BISPHENOL A (BPA) SUB-COMMITTEE

DR. MCNEIL: Sidebar here -- I think what we'll do then -- We were hoping to have Garret FitzGerald join us right at the beginning, but rather than delay the start of this important session, I think we'll ask Dr. Philbert to make his presentation.

Dr. FitzGerald, who was a member of the sub-committee, will join us by phone as soon as he can, and we'll try to get him on line now.

And again, I'd like to express my gratitude and that of the Science Board to Dr. Philbert and his committee for their hard work. They met many times. They have talked on the phone many times. They wrote and re-wrote.

DR. PHILBERT: I'd like to thank Dr. McNeil and the Science Board for taking my first meeting on the Science Board to immerse me in such an easy issue.

The sub-committee was charged with the scientific peer review of the draft assessment of Bisphenol A for use in food

contact applications, and as such, our charge was two-fold. A) to focus solely on the draft assessment and to provide a scientific review and not a risk assessment, per se, or a risk management.

So, the process is as follows. We were a temporary sub-committee constituted by this Science Board to look again at the scientific peer review of the draft assessment produced by the FDA, focused only on Bisphenol A for use in food contact applications. The sub-committee was composed of two Science Board members and augmented by five scientists from academia and government agencies.

Members of the sub-committee were chosen for scientific expertise in disciplines related specifically to the issues addressed in the document.

I apologize for the small type, but this table, which is available in the handouts, shows the dates of our teleconferences, when materials were provided

to us for review, and highlights the September 16 public meeting that was held in this hotel, followed by another telephone conference on October 10, a subsequent conference on October 16, and culminating in this oral presentation to the Board.

The review of the document encompassed an in-depth look at the processes and the scientific methods, et cetera, that were employed in the production of the FDA assessment. On the 16th of September of this year, we held a public meeting, as I had mentioned earlier.

I'd like to extend very special thanks to Drs. Tarantino, Bailey, and Twaroski, who provided us with a clear and concise overview of the processes that they used in producing the document. I would like to extend a special thanks to Dr. John Bucher from the National Toxicology Program, who laid out for us very clearly the framework that was employed in evaluating studies that went

beyond the laboratory practice studies.

Dr. Frederick von Saal kindly came and gave us an overview of the findings of the Chapel Hill Bisphenol A expert panel, and the findings specifically that diverge from the FDA draft assessment, and I again, would like to thank them all for taking the time to come and inform us on this important matter.

We had open public hearings followed by an invited panel of experts, and that's provided in the first appendix to this sub-committee report, and I'd like to extend my thanks to them.

The individual comments of the sub-committee were complied by myself in late September. The draft report was discussed extensively both through e-mail and one on one teleconferences and the joint teleconferences as indicated in the table. It was finalized and submitted on the 20th of this month. And I'm happy to report that the report represents consensus. There is no minority report, and

I'm gratified to say that I've been on other panels where the subject matter has been much less contentious and had much more vigorous discussion. There was great accord even though there was very deep examination of the individual's issues as they arose.

So, the FDA report scope is abstracted as follows, and there are many other more minor points that are encapsulated in the documents and I encourage everyone on read it carefully.

Bisphenol A is clearly present in food contact applications results in dietary exposure of Bisphenol A to infants, children, and adults. And the sub-committee agrees with the focus of the FDA draft assessment on dietary exposures in children largely because they are more likely to have greater exposures and because of the metabolic state of development of the liver -- and specifically with respect to the development of sulfotransferases and glucuronidases, and the

relative lack of activity in an infant liver -- they're more likely to have susceptibility to the parent compound.

Food consumption patterns in infants clearly expose them to a greater amount of the material. Metabolism, as I've just mentioned, and given some of the newer studies on development of the sexual systems and of the nervous system, there may be vulnerability due to a variety of mechanisms.

With respect to our findings, we suggest that the assessment would be strengthened by considering cumulative exposures and differential risk in neonates. There is a commonly held assumption that dietary intake is the major route, but there is precious little data substantiating other potential routes of exposure, and a placement within that full range of exposures of the dietary intake.

Thus, exposure assessment in the document has important limitations. As has

been mentioned earlier, the rather small number of infant formula samples that were taken to underpin the report we found was inadequate.

It also relies on mean values rather than accounting for variability in samples and stratifying the amount of Bisphenol A into quartiles or quintiles for matching up with an epidemiological study.

The draft assessment does not articulate reasonable and appropriate scientific support for the criteria applied to select data. I.e., there was no apparent framework in the draft assessment that allowed for evaluation of inclusion of studies or exclusion of studies. And so, we subsequently came to the conclusion that we do not agree that all non-GLP studies should be excluded from use in the safety assessment.

The FDA should use those studies that are judged as adequate by NTP, CERHR, or "SEER," in the hazard dose response and safety

assessment of Bisphenol A.

And here, John Bucher's presentation was incredibly helpful in laying out the consistent method for appropriate evaluation of studies rejected by the FDA, and for inclusion in the CERHR assessment.

Several additional studies of effects of BPA on adult humans and animal species published after the completion of the draft assessment should also be considered for inclusion in the final assessment. And in our report, we note the limitations of many of these new, sometimes smaller-scale, mechanistically-focused studies, including route or exposure, dosing regimes, and statistical design of the studies. Nonetheless, we feel that they may inform the assessment process.

We also found that the draft assessment lacks an adequate characterization of uncertainties in its estimates of both exposure and effects, and that the weight of

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the evidence provides scientific support for the use of a point of departure substantially lower than the 5 milligrams per kilogram body weight per day that was calculated in the draft assessment. And in order to arrive at that assessment, one includes studies identified by CERHR as adequate in having utility.

Available quantitative and qualitative information provides sufficient scientific basis to conclude that the margins of safety defined by FDA as "adequate" are in fact not adequate, including the application of uncertainty factors. And to be clear, the sub-committee focused here on exposure in infants. Also to be clear, relies on the Tyl et al study is understandable, is warranted, and is sound for use in quantitative risk assessment.

Now, the problem here is that state-of-the-art assessment methods, such as benchmark dose modeling, was not employed.

And so, while use of the Tyl studies was sound, the modeling aspects of the exercise could benefit from greater attention.

So that leads us to the irreducible conclusion that the Tyl studies are not the only studies that can be used in this context. Smaller high-quality mechanistic studies may portend significant health risks at lower exposures than those used by Tyl et al.

Although we were all of a single mind that, while these lay very markers in the field, they do require further attention in terms of much more GLP-type approaches to getting the answer. But what they do allow for is the identification of additional hazard endpoints that are not uncovered in the high quality GLP studies, not because they were deficient, but precisely because they were not designed to find those endpoints. And these endpoints include mammary, prostate, and neural behavioral development.

So, as alluded to earlier, the FDA assessment focused only on food contact applications and therefore did not look at the totality of exposures from other routes, and so it's a little difficult to assess where in the range of exposures food contact applications are pitched.

This is problematic because the data isn't there, and so, really, this is a call for better exposure assessment. Exposure assessment was clearly limited both in size, geography, temporal distribution, and I'm sure others can come up with other caveats.

The exposure assessment does not adequately account for variability in the potential exposures. The point estimates of exposure are used rather than stratifying into, for instance, the 95th percentile.

The small sample size, frankly, also doesn't allow for any in-depth analysis of variability in either the sample that was gained, or in variability of how the food is

prepared -- whether or not individuals microwaved in a polycarbonate container in situ or prepared the formula in some other way.

The draft assessment did not include a sufficiently wide range of samples for estimating BPA contact in food, distribution of data value, sensitivity analysis for data values without distribution, or demographic information to determine the likely number of people exposed at each estimated concentration, i.e. 5 percent of children less than 1 year old are exposed to x micrograms per kilogram body weight per day, which would very much help in the analysis.

There was also no quantification or characterization of the uncertainties included in the assessment, and this represents a lack of a coherent approach to the establishment or quantification of uncertainty and is viewed as a major omission in the assessment.

And here, I would yield to my colleague, Dr. Vandenburg, who thankfully, as we referred to in an earlier discussion, is a risk assessor and saved us from making several mistakes. But the choice of uncertainty factors is tightly interwoven with the study or studies that one chooses to include in the assessment.

And so, that highlights the need for a coherent framework up front for inclusion and exclusion, and then building the uncertainty factors off that.

There was one notable deviation in the report. The draft report selected five milligrams per kilogram body weight per day as the no adverse effect level and identified several uncertainty factors. Ten for reversible intraspecies variability. Ten for reversible interspecies variability. Ten for irreversible reproductive or developmental effects, and ten for systemic toxicity from less than chronic exposure extrapolations to

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chronic exposures. But the stated uncertainty factor in the draft report is ten to the three, and so we concur that this needs to be revisited.

And as mentioned earlier, selection of alternative studies for a point of departure, i.e. based on non-GLP studies would affect the selection of this uncertainty factor.

I want to underline here that the sub-committee did not do an additional assessment, but we reviewed the FDA assessment and we did not think it was appropriate that we engage in an additional assessment, the time constraints not withstanding.

There's also limited data available with regard to other food contact exposures that may be pertinent, especially in infants, i.e. polycarbonate sippy cups, sport bottles, and other containers that are used frequently.

The NTP brief suggests that

neonatal metabolic capacity is far less efficient than adults in animal models, and we think that it's noteworthy that the Tyl studies were not designed to look at exposures in neonates, and that that needs follow-up. However, it's our consensus that this may place neonates at greater risk than is acknowledged in the FDA assessment.

So, in terms of future directions, it's clear that additional bio-monitoring studies are needed and would shed light on other exposures. There's a marked paucity of data on internal dose in vulnerable populations and that's an area for enhanced further research. And this is especially true for infants with additional exposures through medical devices. And these children may be at risk due to an ongoing disease burden. This highlights the need for analysis of cumulative exposure and differential risk in neonates. There is also a need for the development of robust pharmacokinetic models that will be

useful for integrating non-oral exposure routes into risk assessments.

As I mentioned earlier, some of the smaller mechanistically-focused studies use subcutaneous exposures. What that means for a low-dose chronic oral exposure has yet to be determined and can be achieved through PBPK modeling. There needs to be models built for humans, non-human primates, and other species to make the extrapolation more robust.

There will be a need, we feel, for study on non-human primates, but we feel that they should be limited and focused. The resulting PBPK models will address inter-species effects. They will enable strong and accurate extrapolation to humans. They will reduce uncertainties surrounding species-specific endocrine development, and here, clearly a non-human primate versus a rat versus a mouse -- well, that leads to a lot of interpretation. We feel that this will close the gap. This should be question-driven and

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limited due to the expense and of course, ethical concerns with use of large numbers of non-human primates.

The JAMA study, which was released just prior to our September meeting, is also a landmark study. It raises a number of interesting questions that must be confirmed. We suggest that the FDA should seek the plausibility, the biological plausibility of the effects observed in rodent studies and in the human study.

We need to identify links between insulin resistance and Bisphenol A in vivo. We need to ask the question, is insulin resistance due to BPA-linked perturbations in adiponectin homeostasis a robust effect, and does it translate from in vitro to in vivo. Does BPA elevate blood pressure and hence, the response to thrombogenic stimuli in vivo in a dose dependant manner. And are any of these effects influenced by gender. And one might also throw in there, by age and other

biological effects.

We also suggest that large rodent study should be considered to address the central question of the developmental toxicity of BPA, and the study should be designed for regulatory purposes, i.e. it should meet criteria established by FDA or reasonable criteria set by the scientific community for study evaluation. It should address the endocrine mechanism-based concerns of the scientific community, use endpoints and models validated for the study of endocrine-mediated developmental processes.

And appropriate experimental designs in endpoints already exist and should be employed to evaluate effects of endocrine-active chemicals on the development of structure and function of the nervous system and other organs of concern. So, in many ways, there is no need -- the wheel already exists for many of these experimental models and there's no need to re-invent it.

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The experimental design should be statistically robust and there are many statistical models out there that can be used to optimize these studies for use in a risk assessment.

We also recommend that FDA look into the development of meta-analytical capabilities that would better enable the systematic evaluation of disparate, i.e. GLP and high quality, non-GLP mechanistic and descriptive studies for use in risk and safety analysis and assessments.

We suggest that there is applied a limited sensitivity analysis that would summarize the impact of inclusion of appropriately selective alternative studies.

We also are of one mind that, as an akin to the pharmaceutical industry, any data on the safety or risk of BPA generated subsequent to the approval of a product should be released for independent review, either here at this Science Board or elsewhere.

And with that, I would like to acknowledge with deep thanks the efforts, the tireless efforts of the sub-committee, who were enormously responsive. Garret, who hopefully is joining us --

DR. FITZGERALD: I am.

DR. PHILBERT: Thank you. Our Science Board colleague, Dr. Phil Bushnell from the EPA, Antonio Calafat from CDC, who is here today, along with John Vandenberg, Howard Hu from University of Michigan, and Howard Rockette from Pittsburgh. Also, Carlos Pena, who ably staffed the sub-committee. I'd like to thank the FDA for their responsiveness in providing us with the materials and with the help that we required when we needed it, as fast as was humanly possible. Thank you.

Q AND A AND DISCUSSION:

DR. MCNEIL: Well, thank you very much, Martin. That was a wonderful presentation and a very thoughtful report.

So let me tell you what I think we

should do now -- just lay out the order of the rest of the time devoted to the subject.

We will have questions about this particular document by the Science Board. At the end of that time, there will be a series of options presented to the Board for their consideration.

Those options are actually written on paper that you have at your places that we will discuss in a little bit more detail, but just for purposes of the audience at this point, and they will be shown shortly. They basically say accept the report or accept with further input from either the FDA or the Science Board in terms of the need for additional studies. Or of course, there would be other options, but those would be the ones that seem most likely.

If it's accept with further information, that would move decision-making from the Science Board to February. If the report is accepted now with small changes,

that would make a decision possible today.

So, you can see that these are the options that we will be discussing at the end of the question and answer period. And the last two require a little bit of clarification because they may not be worded as well as they should be. And Jack Linehan has graciously agreed to be the scribe for the Science Board in terms of identifying future areas that we come up with.

So, I think, with that, I would like to ask members of the Science Board for questions or comments of Martin or other members of the Science committee, and Dr. Garret FitzGerald is on the line now.

Yes, please.

DR. SASICH: I've got two questions. The first one is -- you mentioned that there was a change in the language in one of the bullets.

DR. MCNEIL: Oh, yes. Why don't we put those up. That's a good question, Larry.

Sorry.

Can everybody see that? If not -- can you all read that? There are actually -- I will read it.

There are two. The last bullet has been edited into two bullets. So, let me read the first one. Here it goes. So scratch the last bullet from the report as you have it, and once I've read this potentially you can see that.

Coupling together the available qualitative and quantitative information, parentheses, including application of uncertainty factors, provides a sufficient scientific basis to conclude that the margins of safety defined by the FDA is adequate are, in fact, inadequate. This does not mean that the potential exposures are not, quote, acceptable, end-quote. The latter is the subject of policy that appropriately rests with the commissioner.

Any subsequent policy decisions

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would benefit from revisions to the draft assessment based on the subsequent report and would be formed by other pertinent considerations.

That last bullet is further augmented by the statement, the weight of the evidence suggests that establishment of a more conservative margin of safety is indicated for infants.

So, I hope that clarifies the clarification of the last bullet, which I think was raised by one of our speakers and I can't remember exactly who.

So, Larry -- Larry, did you have other comments or questions? By the way, we'll make copies of these for members of the audience.

DR. SASICH: No, I see little difference between not adequate and inadequate. I didn't quite understand the necessity of that change.

DR. VANDENBERG: My name is John

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Vandenberg, and I'm here representing the sub-committee and myself. Although I work at the EPA, my appropriate disclaimer is I'm not representing, not necessarily representing the views and policies of the EPA.

As we discussed this particular section, what I would point to is, it says the basis to conclude that the margins of safety defined by EPA. So the construction in which we're working in is that in the draft report, FDA defined what, quote-unquote, adequate meant.

And that was that there was a relationship between the margin of exposure and the selection of the uncertainty factors. So, within that construct, what we have is the realization that that was a margin of about two in the draft when you do the calculations, and that would meet the definition of adequate, as defined by FDA.

So, in our deliberations, what we concluded was, in fact, that a different point

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of departure seemed to be likely if the draft assessment was revised. That would be substantially below the point of departure that was identified by the FDA, and that leads you to the conclusion that that calculation of the margin of exposure to the uncertainty factors would in fact yield not an adequate, but the converse, which is inadequate.

So, we're using the construction as defined by FDA as what adequate means there. And I think its perhaps confusing because adequate is not the same word as acceptable. And the word acceptable rests quite rightly with the FDA commissioner, which is what that next sentence speaks to, is that the decision, a policy decision as to whether or not some particular exposure is acceptable or not certainly didn't rest with the sub-committee. It rests with the FDA commissioner, so that's why the elaboration, I think, has been suggested here.

It's to make it clear that the

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sub-committee is working within the construction of the report. The definitions, as we read them in the FDA draft, and we are not speaking to what is acceptable or not. That's not the role of the sub-committee.

I hope that answers questions.

DR. MCNEIL: Right. The sub-committee is to review the science only.

DR. SASICH: One other quick question. What is the argument for only using GLP studies as it was done in the draft report? What problems could arise from using non-GLP studies?

DR. PHILBERT: Perhaps the most prominent reason is the number of animals that's used. So, in order to get an NIH-style study done, you can use small numbers of animals. You do the experiment as many times as it takes to get the thing published. But a GLP study has much higher requirements for testing of the test article, characterization of the test article, and so on.

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I'm not an expert in GLP studies, but there are much more rigorous reporting requirements, including, as Dr. Hentges pointed out, the idea that if you repeat the study and you get a negative or positive result -- that you report that, too. So the bar is much higher for GLP studies.

DR. PARKINSON: What I also read in the report, Martin, is that the FDA reviewers made a point that in a GLP study, they had the raw data and they could analyze it themselves, as you would with a drug submission. Whereas in a peer review paper, you're dependant on what's presented, as you just pointed out.

I had a question, speaking as an oncologist, because --

DR. PHILBERT: Sorry to interrupt. John, I think, had an amplification on the last point.

DR. PARKINSON: Oh, I'm sorry.

DR. MCNEIL: John, I didn't see your hand.

DR. VANDENBERG: Just regarding the availability of data, at the Environmental Protection Agency. In the risks assessments done at the Environmental Protection Agency, we routinely use non-GLP studies, and if the study is viewed as critical to the assessment, It's not unusual for us to request the raw data from the investigators then.

And generally, if the studies are relatively contemporary time-frame, we've had good success in getting such studies. That then supports the more quantitative analysis. The application of the benchmark dose modeling approaches that we refer to, typically GLP studies, because you do have the full data set, are amenable to various types of quantitative analyses. But that was not done here by the FDA.

DR. MCNEIL: Can I just ask, what does very good luck mean?

DR. VANDENBERG: In terms of getting the studies from investigators that

are non-GLP studies, I would say the majority of the time.

DR. PARKINSON: My -- I think it's a question. Maybe it's just a comment, but in looking at potentially susceptible populations -- and I understand the argumentation for neonates. It was very powerfully made.

There's another potential population that comes to my mind as an oncologist. And that's the population of post-menopausal women on aromatase inhibitors. These new generation aromatase inhibitors essentially create an estrogen-free state. There is a phenomenon called collateral hypersensitivity. These tumor cells become extremely sensitive to very, very low levels of estrogens. I have no idea whether that is relevant to Bisphenol, but it is a setting in which some level of estrogenic activity can definitely effect natural history of the disease.

So, it's just something to raise

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as future studies are prepared. I just couldn't find anything about it as I was teaching myself about this topic.

DR. MCNEIL: Martin, do you have any comment on that?

DR. PHILBERT: No, that's a really good point, and I think any additional language that the Science Board can provide as suggestions to the FDA for inclusion in the next assessment would be helpful.

DR. MCNEIL: Specifically, the effect of BPA on estrogens in chemo -- women on chemotherapy --

DR. PARKINSON: In severe estrogen deprivation states, which the one I'm familiar with, is in the meeting of aromatase inhibition.

Would you agree, Frank? This is your world, also.

DR. TORTI: I will. That's exactly right, and I really appreciate it. Thank you.

DR. CALAFAT: In addition to

pregnant women that one of the speakers previously mentioned as well -- that's one population, sub-set of a population, that wasn't mentioned in the report.

DR. MCNEIL: Does that relate to this comment or is that a separate comment?

DR. CALAFAT: Different. It's for different reasons. It's a susceptible population.

DR. MCNEIL: So the susceptible population so far are the neonates, the estrogen-deprived patients, particularly those on aromatase inhibitors, pregnant women -- of course, others, but those are the ones we just mentioned.

DR. PHILBERT: I would suggest that rather than trying to pull the ones that are upper-most in our mind at the moment, that the FDA go back and have a thorough look at potential susceptible populations, and re-visit the assessment in light of those.

DR. MCNEIL: Okay. Well, let's see

-- I thought -- Oh, yes, Lonnie?

DR. KING: So, maybe you could help me clarify and maybe expand on the finding that uncertainties were not adequately characterized. Could you talk a little bit more about that?

DR. VANDENBERG: Yes. In the draft report, I think what we found was that there was an analysis of the exposure -- I'll break it down to exposure and then toxicological literature, and with respect to the exposure analysis, mean values were selected based on the, really, rather limited sample set for the cans that were evaluated. But there really wasn't any evaluation of the higher percentiles, as was discussed by Dr. Philbert.

So, that's an example of if you were to do an analysis and look at the mean, look at the 95th percentile, it would give you insights regarding the potential for differential exposure based upon that limited sample set.

In the same manner, in terms of the toxicological research, if there was analysis done of alternative points of departure, much as the FDA selected the 5 milligram per kilogram body weight per day, was a single-point estimate. Again, using the benchmark dose approach, you have a way of modeling the dose-response relationship to see how the strengths of the study give you insights on the strengths of that point of departure. Or, importantly, looking at other studies that may be reasonable for the point of departure.

And as you saw from the Committee's perspective, a lower point of departure seemed to be merited when you considered all of the evidence, including the non-GLP evidence in its entirety.

That's what we, I think, meant by a sensitivity analysis, just to give some examples.

DR. MCNEIL: Questions from the

FDA? Oh, I'm sorry, Lonnie. I missed that.

DR. KING: Quick question, and it was in the report, but maybe it's not an important one, but it was about, if I remember, about the use of microwaving, and was that adequately studied or was a real limitation or was this a finding that was not very critical?

DR. PHILBERT: I think it just highlights the fact that people don't use or prepare food in a monolithic fashion -- that there's a wide variety of methods of preparation, which logically leads to the possibility of a wide array of leachates into the formula, and that the uncertainty around that should be narrowed by just going out and measuring it.

DR. MCNEIL: Martin, I just had one question. With regard to the Canadian analysis and report, nothing has come out since your report from Canada, is that correct? That you know of.

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DR. PHILBERT: Not to my knowledge.

DR. MCNEIL: Okay. Erik, please?

DR. HEWLETT: Thank you. I need, as a new member here, I need a point of clarification on authority.

The statement is made in the letter from the NRDC commenting on the definition of safe, reasonable certainty in the minds of confident scientists that the substance is not harmful under intended conditions of use.

My understanding is that, especially focusing on infants and this product as a food additive, that there are a whole bunch of other uses that are -- if this were banned by the FDA, there would still be lots of other sources of this that would not be regulated in the same manner.

Is that correct? So, we're only accounting for a small proportion of the potential exposure to BPA in the topic of this conversation?

DR. MCNEIL: Would you like to address that?

DR. SUNDLOF: Sure, thank you. Yes. You are correct. This only applies to the food additive characteristics of it, so other products that were not considered to be food additives may not have to meet that standard or may have to meet totally different standards.

So if you're a bicycle helmet, for instance, that standard of reasonable certainty of no harm does not apply in that case.

DR. HEWLETT: What does that mean, then, for drinking containers that don't -- are not packaging food?

DR. SUNDLOF: Those are food contacts.

DR. HEWLETT: Because it comes in contact with -- water, even.

DR. SUNDLOF: It comes in contact, yes.

DR. HEWLETT: Okay. Thank you.

DR. TORTI: But just to clarify, Erik, in addition, one of the things that was said earlier but I think is worth repeating is that these other sort of IB2B being alike exposures, just as an example, are not being ignored.

And that we specifically said this cannot be wrapped around, sort of, in one bite, and that we have as an agenda item for future Science Boards to look at other exposures and Dr. Schultz who had to go over to the Secretary's office this afternoon, but made that point this morning as well.

So, it's not as if we don't recognize that these other things have to be addressed.

DR. SASICH: Martin, in the sub-committee report, we were talking about the ability of, perhaps, to use or to develop meta-analytical techniques for looking at these different studies.

The thing that I know usually comes from the medical literature, and I think if, in reading the medical literature, we'd rather have a large, simple trial rather than a meta-analysis to base a decision on.

And, at least in the medical literature, we don't have very good ways of dealing with heterogeneity of results. Are there techniques to be able to handle those things which your comfortable with or are we better off looking at large, simple trials, however that applies in this case?

DR. PHILBERT: As an academic administrator, I can give you the perfect answer, which is, it depends.

No, I think you point out the frontier of the science, frankly, and it's not just for Bisphenol A. It's for a variety of issues that we talked about this morning. Different studies are performed for different reasons, and I think this highlights the need for FDA to have a concerted, focused,