FOOD AND DRUG ADMINISTRATION

CENTER FOR FOOD SAFETY AND APPLIED NUTRITION

FOOD ADVISORY COMMITTEE

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Silver Spring, Maryland

DR. ACUFF: Good morning. I'd like to call the meeting to order again this morning. And we will begin right off with the presentation by the International Association of Color Manufacturers, Sean Taylor.

So, Sean, whenever you're ready.

DR. TAYLOR: Good morning. First of all, I'd like to thank both the FDA and the Food Advisory Committee for inviting us to come this morning and give a talk. We want to talk a little bit this morning, as we said, about the safety and benefits of food colors.

My name is Sean Taylor. My company is Verto Solutions. We're a trade association management and scientific services consulting company. In that role, I act as the scientific director for the International Association of Color Manufacturers. My co-presenter this morning was meant to be Dr. Joe Borzelleca from VCU School of Medicine. Joe has had a family health

issue that has prevented him from coming this morning, and he offers his regrets.

What we'd like to do in our talk this morning is talk a little bit about our association, just roughly, what we do and why we think what we do is important; talk a little bit about the history of FD&C colors, the use, the legal status, how they became the FD&C colors; and then talk about the safety of them, as well.

I think we'd like to talk just a little bit about why we think that colors have not been proven to cause hyperactive behavior, and I think we've heard a lot of testimony over the last couple of days that's very interesting.

I want to stress my background is in biochemistry. I'm definitely not a behavioral psychologist. And so when we're talking about this, we're really relying on the opinions of experts who have provided opinions that we've been able to find and look at. So I have to admit my knowledge about how some of these studies are done and the complexities, which I think we saw yesterday -- these are very

complex studies -- is somewhat limited, but I'll try and do the best I can.

Then, finally, I think we'd like to talk a little bit about colors, why we use them, how they're used in terms of labeling, as well, why we think that's important.

So what's the role of the International Association of Color Manufacturers? We actively represent the interests of the color industry. The way that we do that is we demonstrate the safety of color additives. Essentially, the food industry and the color industry wouldn't be able to sell products if they weren't considered to be safe, if there was major concern about them from the FDA.

By doing this, we promote the industry's economic growth. We participate in new color approvals. We work on regulatory and legislative issues that affect the industry worldwide.

Related to the color approval issue -- and I'll come back to this in just a few minutes. But I think yesterday there was a question about how come there haven't been any new FD&C colors approved since

1970-something, and it's a good question.

I think what you'll see this morning is there's a pretty high bar to put a new color additive on the market. And in a lot of cases, it's economically just not worth it, because we have good alternatives, either currently approved FD&C colors, or in some cases the exempt from certification or what someone called naturally derived colors.

So the lack of new approvals doesn't necessarily represent the fact that there isn't a lot of interest in doing this. It just means that there is such an extensive amount of safety testing that's required and so much data needs to be provided, but there really isn't necessarily an economic incentive to put new FD&C colors on the market right now.

The members of ICM are diverse. It includes some really very small family-owned companies here in the United States, some larger color companies in the U.S. and worldwide. We also have members that are consumer product companies that are all interested in making sure that these color products are safe.

In terms of that -- and we heard yesterday

from Dr. Cheeseman a little bit about the legal framework. But what we heard yesterday is that colors are food additives under the 1958 Food, Drug, and Cosmetic Act. All color additives require premarket approval in the U.S. via color petition process. So you don't put something on the market -- our companies don't put something on the market until it goes through this very extensive premarket process.

Ultimately, if the colors are considered to present no significant safety issues, then they're listed in the U.S. Code of Federal Regulations under Part 21, CFR Sections 73 and 74.

So what do we mean by certified and exempt colors? And hopefully this is a little bit educational, because you probably hear the term "certified" and what does certification mean, what does exempt from certification mean.

Colors generally can be divided into sort of two categories in the United States, either certified colors or exempt from certification colors. The certified colors, each batch, as we heard yesterday, is tested by an FDA lab, the FDA color certification group

does this work. They are funded by user fees. This is not industry testing. It's FDA testing. That confirms the safety.

Now, when we say confirms the safety, what do we mean? We mean that the specifications of the material are analyzed. Does it meet purity specifications? Does it meet certain specifications related to the presence of secondary components? Are they below legally required limits? Other issues. Does it meet the sort of standard heavy metal limits that would be in all food addictives?

Exempt from certification colors are those that don't require that sort of individual batch testing. Now, you might ask the question, well, why do some colors require this, but others not, and a lot of this is really related to the historical providence of where these colors came from.

I think, as we heard a little bit yesterday, certified colors were originally isolated from coal tar. If you take, for instance, a little bit of -- a drop of oil or coal tar, and you spread it out on chromatography paper and sort of let it divide out,

you'll see this sort of rainbow of colors. And each of those colors was a dye that was originally isolated.

I want to stress, these are not now produced from coal tar. We heard yesterday they were produced from petroleum products. In fact, they are produced from organic chemicals in the same way that pharmaceutical products, for instance, are synthesized.

The exempt colors have in many cases a history of use. They have a natural occurrence, potentially in food, and because of that, there was less concern about the specifications, about the presence of other secondary components. And so there was no, to my understanding, real urgent need, in the opinion of the FDA, for batch testing for each of those.

The certified colors are the FD&C colors. And when we're looking at those colors, we're going to focus this morning, I think, on only those colors for which there's real certified volume that's been reported over the last couple of years.

The petition that was presented to the FDA includes I believe orange B and Citrus Red number 2. There really isn't any significant volume that's been

reported in certification of those colors over the last couple of years.

The colors that we'll really focus a lot on, because these are also, I think, the focus of some of the hyperactivity causal relationship studies that have been done, are FD&C Red 40, Red 3, Blue 1, Blue 2, Yellow 5, Yellow 6, and Green 3.

Now, when these colors are not certified -- and if they're not certified, they would not be allowed for use in the U.S. But when they're not certified, they have common names that are shown on the right, allura red AC, erythrosine, brilliant blue, et cetera.

There was a question yesterday, I think, related to color intake and the per capita intake, and I think there was some data that was presented that suggested that the per capita intake of these FD&C colors has increased very dramatically in the U.S. And I think that's a pretty important point to address.

In a lot of ways, this FD&C color certification that's done is a gold standard throughout the world at this point. The color testing that's done

on each of these individual colors is very extensive. The FDA Color Certification Lab has real experts in analytical chemistry.

As a result of that, companies throughout the world will often produce or, in some cases, have product made available for batch testing here in the U.S. that's reported as certified color volume. But that volume is not necessarily the amount that ends up in the U.S. food supply.

So when we're looking potentially at 6 million pounds of FD&C Red 40 that was certified in 2010, that doesn't mean that there's 6 million pounds of FD&C Red 40 that ends up in the U.S. food supply.

Now, what is the exact number? What's the correction factor? To be honest, I don't have a good number. Is it 30 percent that goes back out of the U.S.? Is it 60 percent? Is it 50 percent? We really don't know. The color certification numbers, the figures are confidential. It's confidential business information.

I think that we would very much like to try and refine those exposure estimates with the FDA based

on potentially some surveying of our members and of the larger color industry, as well, to try and find a much much more realistic number for that estimated daily intake.

So those are the certified colors. The exempt colors -- and you can see here there's quite a few of them under 21 CFR 73, and they kind of run the gamut from things like Annatto extract, which is very commonly used to color cheese rinds and certain cheeses, to caramel colors, to beta carotene, grape skin extract. There are some fruit juices and vegetable juices that are approved for use provided that they're from an edible fruit or vegetable from a plant and very minimally processed. Saffron is a color, et cetera.

So how do these colors list -- let's say you're a new color manufacturer and you have a product that you'd like to bring to the market. And this happens from time to time, where an existing color manufacturer who hasn't done an approval in a long time will come and say, "What do we have to do to get this thing on the market? How quickly can we make this

happen?" When those calls come, the simple answer is it's not going to happen anytime soon, because this is a very exhaustive, very thorough review.

The color added petitions that are filed require information about specifications of the material, the purity, secondary components, the potential toxicological properties of those; questions about the use. There's a technological justification for the use of the color, how it will be used; toxicological data according to FDA Redbook requirements, substantial potential exposure information. And let me stress again, this is a premarket approval, so this is going to be an estimated exposure at that point.

The FDA will review that preliminary information. It would be common, I think, for sort of a preliminary meeting to sort of begin guiding what sort of testing would initially be required. The applicant would submit information into the FDA. The FDA would respond, very common task, for additional information. There's sort of a public review. This would go into the Federal Register as a potential final

rule eventually, so there are public comments allowed.

It's a very transparent process, I think, in our opinion, and there's a lot of opportunity for public airing of questions. Academicians were involved in many of the questions related to the FD&C colors and some of the other colors throughout the years. It takes time. It's expensive as well. But that's sort of beside the point. The major point here is there's a long, thorough process of vetting before these things are allowed to be put onto the market.

Specifically, what's required? And if you sort of try and roughly look through the FDA Redbook, and based on whether it would be a low level of concern, an intermediate level of concern, or a high level of concern, most of the FD&C colors and some of the exempt colors, as well, sort of fall into that intermediate or high class.

So what type of test were we looking at specifically? Genetic toxicity tests; we'd be talking about in vitro tests, like bacterial reverse mutation, Ames assays, mammalian cell genotoxicity tests, chromosomal aberration, mouse lymphoma, micronucleus.

Back when several of these were studied, they would commonly look also at things like sister chromatid exchange. In vivo, it would be pretty common, I think, back in the era when this was done, to look at unscheduled DNA synthesis, micronucleus type experiments.

Short-term toxicity tests were pretty common. So we have good LD50 data for a lot of these colors, or for all of the colors. I think we would recognize, and most would recognize, that LD50 data doesn't necessarily provide you a whole lot of insight into the long-term safety. But that isn't really a problem here, because we've also done sub-chronic studies, 28-day studies, 90-day studies in rodents, in some cases, in non-rodents. We've done preliminary short of short-term -- or I should say, one-year toxicity assays. And then for all of the FD&C colors, we have a very extensive jacket of chronic data. We're looking at two-year carcinogenicity studies, in some cases, lifetime bioassays. We have repro data, we have developmental toxicity data.

I think yesterday there were some questions

about whether there is really much pharmacokinetic data that's known for these colors, what's out there. And I think what I would say here is for the FD&C colors, we actually have quite a bit. We have a very good understanding of the metabolism. We have a good understanding of the pharmacokinetics.

Related to that, I think what I could say, as we begin to think about biological mechanisms, we have a good understanding that these colors do not have a significant lifetime in the body and that, in general, they are not well absorbed. The one exception to that, I would say, is we do see more absorption of FD&C Blue Number 1 versus the other FD&C colors. So that's definitely a variation. But we think we have a pretty good handle on the metabolism on the ADME studies that have been done in pharmacokinetics.

Now, in some cases and for some of the colors, there have been follow-on studies, some human studies that have been done, generally, not as part of the color additive approval process, but, as I think we've seen over the last couple of days, human studies are certainly being done on some of these colors.

So this very substantial safety data set for many of these colors has ultimately, I think, led to the FDA review that's led to the listing of these as allowed colors under 21 CFR, but have others looked at them as well, because you always like to know if your color, obviously, is going to hold up under scrutiny in other parts of the world.

The World Health Organization, U.N. Food and Agricultural Organization, specifically the Joint Expert Committee on Food Addictives, has reviewed all of the FD&C colors, and they through that process have established acceptable daily intakes.

I'll point out that JECFA has just begun to reevaluate these colors. The first colors are coming back for reevaluation at this coming meeting in 2011, which I think will happen in June or July, and we've submitted data to JECFA for that.

Additional data over the years has been collected, not necessarily by the industry. These aren't industry-sponsored studies, in most cases, but researchers continue to be interested in looking at food colors because they are a common food ingredient

throughout the world.

So there are genotoxicity studies that have been published within the last even year and over the last 20 years. We've looked at allergenicity studies. There have been other studies. And as part of the sort of ongoing review at JECFA, those studies are often looked at as well to ask could there be anything significant here that we should be concerned about.

Most recently, the European Food Safety Authority has evaluated or reevaluated the colors. Now, I should say they did this on the basis I think of the Southampton study. I'm sorry. To clarify, they prioritized the review based on the Southampton study. So the first colors that they looked at were those six colors that were within the Southampton study.

Only three of those colors, the FD&C Red Number 40, Yellow 5 and Yellow 6, are actually approved for use in the U.S. The other three, which were carmoisine, Ponceau 4R and quinoline yellow, these are not allowed in the U.S. for use at all.

But nonetheless, EFSA evaluated these colors, and in some cases they've asked for additional data for

what would be FD&C Yellow Number 6, which is sunset yellow. They've asked for an additional 28-day study on the basis of some new information in India. Our industry is working to respond to that request.

In some cases, they've changed the acceptable daily intakes, not, I should point out, on the basis of the Southampton study, but generally on the basis of reevaluation of existing data. There were some cases where the no observed adverse effect levels that were initially decided have now been revised by the new EFSA panel.

Anytime an ADI has changed, anytime there's an additional request for data, our industry looks pretty carefully to see are there going to be any issues that we have to be concerned about here, and certainly everybody says, "Well, how much is this going to cost? What does this mean long term?" But I think the significant issue here is that it really underscores that these are sort of living evaluations. These things aren't on the market and just completely ignored. People are still looking at the safety of color additives, and I think the last couple of days,

we've seen that as well.

Very briefly, just real quickly, let me run through some of the data that we have, and I won't go into any details here. I'd be happy to share that with all of you. It would take several hours, of course, to go through all the data.

But just to give you a little bit of a feeling for some of the FD&C colors for which there is volume reported in color certification, Blue 1 and Green 3, brilliant blue FCF and fast green FCF, were both on the market since about 1929. They were provisionally listed because they had that prior market presence and then eventually were formally listed under 21 CFR.

We have a good batch of data here, in vitro and in vivo gene tox for both. We have rat acute and subchronic data. We have chronic carcinogenicity data in rats and mice. We have repro developmental teratogenic data in rats and rabbits.

For these two in particular, we have a lot of ADME data, particularly for Blue 1. As I said, the absorption is a little bit higher for that color relative to the others; a very low absorption for Green

Number 3. That data has primarily been collected in rats. And JECFA has established acceptable daily intakes on the basis of essentially the same data set that the FDA looked at.

For Blue Number 2, indigotine, it's not certified. It's also been in use for quite a long time. Again, a very substantial amount of data available; in vitro and in vivo gene tox data, acute, subchronic, chronic carcinogenicity data in rodents, rats and rabbit data in reproductive and teratogenic studies, again, a significant amount of absorption, distribution, metabolism, excretion, and pharmacokinetic data that's available in rats.

This is an interesting color, as well, in terms of the reevaluation process, because EFSA has just, I think a week or two ago, come to the industry and asked if we would do an additional in vivo micronucleus study. So what they've done is they've gone back and they've looked at the existing gene tox data, and they've said one of these studies was not done according to the standard guideline, the OECD guideline to do in vivo gene tox studies. So they've

now come back and they've asked us to do a study according to standard guidelines.

I think that's an important point for us because we recognize that if studies are done not using some sort of standard guideline, it can be difficult sometimes for regulatory bodies like EFSA to really say whether it's a valid study or not. So it's our intention to provide that data back into EFSA.

Red 3, again, a lot of data here. Red 3, obviously, there's a lot of interest in the thyroid, and so there have been some special studies done on that; ADME data related to that in humans as well; relatively low JECFA ADI. And Red 3, of course, is used in very, very low amounts here in the U.S. and in other parts of the world.

Then we come to the Azo dyes, Red 40, FD&C Red 40, FD&C Yellow Number 5, and FD&C Yellow Number 6. You can see FD&C Red Number 4 is sort of the newer member of the FD&C colors in use since about 1971 on the basis of safety concerns about another red dye. So it was essentially the replacement.

Along with the FD&C Yellow Number 5 and Yellow

Number 6, there is an extensive battery of testing and a substantial body of data that's been collected; gene tox data, acute data, subchronic data, chronic, carcinogenicity, whether we're talking about a two-year bioassay, or in some cases, lifetime bioassays; repro, developmental data.

For FD&C Yellow 5 and Yellow 6, there's been a fair amount of allergenicity data that's been collected due to specific concerns related to allergenic effects for some of those colors; and, then, ADME data, good data in dogs and rats for Red 40 and good data in humans and animals, we would say, for Yellow 5 and Yellow 6, on the basis that JECFA has evaluated and established acceptable daily intakes for these colors as well.

So that gets us to an interesting point here. And maybe I should go back and say you may ask yourself why did I put Blue 1 and Green 3 on one slide and why did I put indigotine on another slide, and Red 3 on another slide, and put the Azo dyes on a slide all by themselves.

I think one of the things that it's important

to point out here is that the pigments structurally, chemically are fundamentally different. And so when we're talking about biological mechanism and thinking about different plausible mechanisms for whether these would cause effects, it's probably going to be pretty important, I would say, to ferret out whether there are fundamental reactivity differences, because if we're talking about potential binding to a biomolecule, whether we're talking about some sort of actual reactivity that we haven't thought about before, that hasn't previously been studied, it's probably going to be pretty important, I think, in my opinion, to make sure that we're looking at structurally-related substances.

I think that is, I think, one of the real interesting things about the Stevenson work, the Southampton study, and that they really focused on a specific chemical class here of pigments. We certainly have some criticisms about the way the study was done or I should say, experts have some criticisms, but I do think one of the values of the Southampton study was the fact that they didn't just try to throw in all of

these different chemical classes and try and ferret out effects.

At minimum, even though it's still a mixture and even though you probably still can't develop firm conclusions about any of the individual colors, it does seem to be more directed toward the Azo dyes. And I think that has had an impact in terms of the way the Europeans, for instance, have approached the labeling issue with colors.

So let's go back a little bit, and please remember, again, that I'm a biochemist with potentially behavioral problems, but very little experience in behavioral psychology.

[Laughter.]

So what we're going to do is we're going to put up what we've seen from other published opinions about specifically the Southampton study. Before we do that, though, let's say, some research has clearly suggested a link between intake of food colors and hyperactive behavior in children.

The data I think is very difficult to interpret. We heard a really, I thought, very

interesting talk yesterday from Dr. Schab, but I have to admit it left me very confused, because I think this is a very complex series of studies that have been done. They haven't been done using any sort of standard, method, and it can be really difficult, I think, to necessarily know how to place weight into any of the studies.

We heard some discussion yesterday about the Feingold diet and the potential value of elimination diets. And then of course we've seen the work presented by Dr. Stevenson yesterday, the Isle of Wight study, for instance, the Southampton study.

I think we'll focus specifically on some of the work from the Southampton study. The FDA, I think in their interim report, has already reviewed a lot of the studies from the 1970s and 1980s that were discussed yesterday, as well, by Dr. Schab.

I think the general opinion, at least at the time, from the Nutrition Foundation were that there were no significant links between the intake of food colors and hyperactive behavior. The NIH and the National Research Council similarly found no

significant links between the intake of food colors and hyperactive behavior in children.

But let's look at the Southampton study. I would say that it is clearly the most robust and extensive study that's been done to date. A lot of children were in that study. A lot of children were in the Isle of Wight study, as well. What have others said about it? And these are things that we pulled out -- we could attribute all of these to individual reports, and I'll point out where these references came from in a few minutes.

But what were some of the limitations that were identified within this study? And one of them was an undefined time for drink consumption. And I think, to some extent, Dr. Stevenson may have answered some of these questions yesterday. We weren't able to change our presentations in the evening. So if some of these questions have been resolved, I think that's good. But these were certainly questions that we had and others have had upon reading the paper.

So in terms of an undefined time for drink consumption, there was definitely some time variation

between the additive intake and the assessment of behavior. And what is the relevance of that? And if a child drank the drink in the morning and the behavior was assessed six hours later, was the effect smaller than it could have been? Was it larger than it could have been? Was it related to other things? And, of course, we just don't know.

Dr. Stevenson yesterday talked about the complexity of trying to adjust for body weight, and I think that is a significant and difficult issue that would have to be dealt with. But I think ultimately what it meant was that the dose couldn't necessarily be adjusted per child, and so there wasn't a simple way to sort of control or adjust for a milligram per kilogram body weight effect and to see whether there would be relevance there. Potentially, there could be small children that drank the same amount of something that larger children did.

Behavior assessment data -- and, again, I apologize if I can't quite understand the study, but I think what others have said is that the behavior assessment data wasn't necessarily collected for the

respective placebo phases. So there was a lot of discussion yesterday about weeks 2, 4 and 6. And I think what that would suggest is there maybe wasn't the same amount of assessment data that was collected in weeks 1, 3 and 5, which were the weeks when there weren't these specific challenges.

I think the conclusion there is that there wouldn't be an easy assessment of intra-individual variability, because you don't have that sort of baseline data in those non-treatment weeks.

What we've seen from others is that the observed effects lacked, in some cases, clear statistical significance, because there doesn't seem to be consistency within the results across both age groups, across the additive groups.

The behavioral changes, in the view of some, were only partially significant. I think some people have suggested that the increase in hyperactivity or hyperactive behavior was somewhere on the order of about 10 percent. And I think it's a really interesting question, what does that really mean?

I think that the methods that Dr. Stevenson in

his global hyperactivity audit that he's using, to a layperson, they look very interesting, because it seems to be a really comprehensive way to assess hyperactivity. I think it would be very nice to see if there would be some way to sort of validate this type of study approach, and it could be a way forward to develop sort of standard guidelines for doing behavioral challenges with not just food additives, but with everything.

The statistically significant effects -- and let me stress, I say very weakly here, but there were clearly statistically significant effects. They were only measured under a constant seven-day treatment period. And I think it would be an interesting question to ask, would longer exposure exacerbate or eliminate these subtle effects and are these effects transient or persistent.

This is, I would say, way out of my expertise area, but there was some discussion yesterday about if you would try an elimination diet, could you then reintroduce foods. Do children sort of have an initial tolerance or lack of tolerance or something? And I

think the work that could follow from the eventual conclusions from the Southampton study could potentially probe some of these issues.

Now, one of the things that I think is most intriguing from the Southampton study isn't necessarily the study itself. I think that is intriguing, but because of my background as a biochemist, I was very interested in the paper that was published in, I should say, 2010 -- that's a mistake on my slide -- by Dr. Stevenson related to a potential biological mechanism.

Within the Southampton study paper, of course, there was no biological mechanism that was reported. I think what we heard yesterday was some discussion about the possibility of some single nucleotide polymorphisms which may cause a potential exacerbation of the effect, if the effect is there, and I think that's pretty interesting.

Let me go back to what I said just a few minutes ago, which is this study focused very specifically on six dyes, six Azo dyes, all of the same sort of chemical class. It might be very interesting

to see if there is any relevance to look at other types of chemical pigment types and to see whether a similar biological mechanism could be asserted. That said, I recognize that these are very difficult and very costly studies.

I think one of the things that we saw in one of the reviews that was written, that there were low mean levels of observed hyperactivity compared to inter-individual variation, as was measured in other studies. And I think there's clearly a caveat there, which is how valid are those other studies. They probably didn't necessarily have the same statistical power as the Southampton study. But, certainly, I think that's a question that would be valuable to address.

The behavioral changes, clearly, they didn't occur in all children in any one group. They didn't occur uniformly across all age groups, and they weren't necessarily in an even manner for the intake of all additive groups. So I think, without question, there was slightly amended behavior observed in all groups given the additives versus placebo. I don't think

there's really a lot of question about that.

You could argue about what the statistical significance would be, how large the standard deviations are within those types of measurements. I think the take-home message here, though, is that this doesn't necessarily lead to the conclusion that the additive mixes, and specifically I should say the color additives within those mixes, cause an increase in hyperactivity.

There were, I think, pretty intriguing questions that were brought up yesterday about the role potentially of sodium benzoate, about whether there are other things that could be accounted for that would lead to these types of results, which may or may not be dependent on the color additives. I think ultimately, I don't think the question has really been resolved. I think the study, to a layperson like myself, is an interesting study and it's a worthwhile study, and I think it calls potentially for some more follow-on work to be done.

Because of that, again, I think this is a very robust study, but it's difficult to draw extensive

conclusions. And, obviously, a big part of the challenge here is to try and extrapolate results for individual color additives, including some that aren't even part of this group of Azo dyes, to the study of mixtures or to the study of other additives of preservatives.

I guess this is more my personal opinion, to some extent, but we tried to interpret -- perhaps we misinterpreted parts of the study, but I think what this really means it would be really nice if there was a standard guideline for doing this type of behavioral challenge study; if there was some way to say we have good historical controls, we have validated methods.

I'm not trained as a toxicologist, but since I've been working with the food industry, I've looked at plethora of toxicology studies, and every study that's done that is submitted to a regulatory authority follows generally an OECD guideline, sort of a way to say this is the right way to do this study.

I think one of the challenges, particularly with these types of behavioral studies, is it is difficult to develop those guidelines. It's difficult

to do validation to make sure that the results are reproducible, but I think, hopefully, this is where this field is headed, that we are headed toward more of sort of a standard guideline approach. Again, that's sort of my personal layperson opinion.

So what you just saw were several sort of specific questions about the study that were specifically addressed within the various reports from primarily European groups, I will point out just a few of them, and also including a group from Australia.

So some of the things I've mentioned just previously came from the European Food Safety Authority, which I'll talk about in a second, the Norwegian Food Safety Authority, the German Federal Institute for Risk Assessment, which is abbreviated as BFR in German, Food Safety Australia-New Zealand. There are others. In the interest of time, we won't go into that.

The EFSA opinion, I think, though, is a really important one, because we heard yesterday from Dr. Stevenson that I think shortly, very shortly after the study was published, he was asked to provide all of

his data to the European Food Safety Authority so that they could carry out a review. And the review was specifically done by the EFSA AFC panel. And this is the panel that, at the time at least, was composed of people looking at food contact materials, colors, flavors, and other food additives. And that panel has since been dissolved and sort of broken up due to their heavy workload.

But at the time the AFC panel evaluated this, the majority of the people on the AFC panel were also toxicologists, biochemists, medicinal chemists, not experts. So what they did is they brought experts in behavior, child psychiatry, and allergy statistics to help them review the study and to come to conclusions.

These are the conclusions, and, actually, Dr. Stevenson I think presented these yesterday. The study provided limited evidence that the mixture of additives tested had a small effect on the activity and attention of some children. The effects observed were not consistent for the two age groups and for the two mixtures used in the study.

The findings in the McCann, et al, study,

which is the Southampton study, cannot be used as a basis for altering the acceptable daily intakes. That was the opinion that they published, I think it was back in 2008.

In subsequent years, they've been reevaluating these colors, each and every one of the Southampton colors, and within every single one of the opinions that they publish to reevaluate the colors, they reiterate these conclusions. So I think they're still standing very significantly by the fact that they don't view this as something that, in their eyes, would require an alteration of the acceptable daily intakes.

I noted some of their questions about the study. Specifically, though, I will point out that they said the inability to pinpoint which additives may have been responsible for the effects observed in the children, given that mixtures were used and not additives were tested, is a significant limitation.

Again, I think it is intriguing and interesting that the focus was on Azo dyes and not just on all of the different potential chemical classes that pigments are found in. But, again, looking at mixtures

versus individual additives is I think challenging in terms of drawing conclusions.

EFSA found that the findings could be relevant for specific individuals that show sensitivity to food additives, in general, or to food colors in particular. And I think that opinion has now also been echoed by the FDA expert review.

I think there's another interesting question here, again, related to how widespread such sensitivity could be in the general population. I think yesterday Dr. Stevenson presented what, again, I think is very interesting work related to potential biological mechanism and histamine conversion or histamine levels and single nucleotide polymorphisms.

I think we heard yesterday or last afternoon that Dr. Arnold suggested that potentially up to 60 percent of people might have the susceptibility to exacerbation of hyperactive effects for food colors. So there is this potential implication that it could be a much larger general population issue. I think we just really don't know at this point, and I think that will be interesting data to collect.

I think as we begin to address whether there are biological mechanisms that we can relate back to, there are a lot of really important questions that need to be asked, certainly related to these histamine single nucleotide polymorphisms, but maybe some more fundamental questions related to are we really talking about a neurological effect here. And maybe the first question to ask -- and we have some preliminary data for this -- is do we expect that colors, when they're eaten, cross the blood-brain barrier.

What do we know about that? We don't know everything about that. The best data that we have generally is from animal studies, and we all know that animal studies are not perfect models for humans. But what we can say is we know that Red 3, for instance, binds to a specific plasma protein, and that complex is very large. It does not cross the blood-brain barrier.

We know that the brains of rats that have been studied in toxicology tests don't show any levels of significant amounts of dye or any of the metabolites. So there is some preliminary suggestion that in dietary studies and, presumably, in humans, as well, and even

in children, which have somewhat different blood-brain barrier properties compared to adults, there doesn't seem to be any significant amounts of these things that get to the brain. The dyes generally, these FD&C colors, are very rapidly excreted in the urine and the feces.

Ultimately, I think the significance of the effects on the behavior of the children, in EFSA's opinion, was unclear since it was not known of the small changes in attention and activity observed would interfere with schoolwork or other intellectual functioning. And this is their opinion.

We heard yesterday, I think, Dr. Stevenson, in his opinion, he said, clearly, this is a noticeable effect, and I'm just not expert enough in this area to know. So I'll leave that there.

But then, finally, the panel noted that the majority of the previous studies used children described as hyperactive, and these were, therefore, not representative of the general population. And I do think that is one of the great benefits of the Stevenson work, which is it begins to look at some

general population issues.

Norwegian Food Safety Authority, I'll run through these fairly quickly because they're generally consistent. Increases in hyperactivity reported in the Southampton study after children were challenged with artificial food colors were considered small, but not insignificant. The findings were not consistent between the two age groups and the two mixtures. There was limited support to an increase in hyperactive behavior from the mixtures of artificial food colors and sodium benzoate.

The BFR, this is the German Risk Assessment Institute, they suggested that the findings suggest indications of a possible association between the intake of specific food additives and increased hyperactivity. They noted that the observed effects were low compared with normal inter-individual variation. And I think specifically they said the behavioral changes don't occur in all children in the group nor do they occur in a statistically significant manner in all age and additive groups. The trial doesn't supply clear evidence of a possible causal

association between additive intake and the observed effects. And again, they suggest there's no biological mechanism, and I think we heard yesterday there's some pretty intriguing information that should be looked at more thoroughly.

One of the things that came out from the German report, which I put in red here because we'll come back to it, is that additives must be listed on the label of packaged foods. This means that consumers wishing to avoid any intake of the additives, concerned for precautionary reasons, can refrain from consuming these foods.

Similarly, Food Safety Australia-New Zealand concluded there were no public health and safety concerns due to the results of the study and no public health and safety risk from the consumption of foods containing added colors as part of a balance diet.

I think it's important here, FSANZ actually did a color exposure survey when they were doing this work, and they asked the question, how high is the exposure of colors relative to the JECFA evaluated ADIs? And what they found uniformly for the FD&C

colors that are approved for use in Australia is that they're actually very low. The levels are significantly lower than the acceptable daily intakes.

What have other experts said? And let me stress, this is not specific to the Southampton study. This is more generally. Attention deficit disorder association, no research proving that other treatments, such as neurobiofeedback, nutritional supplements, hypnosis, visual therapy or changes in diet, are effective in relieving ADHD symptoms. I think we've heard some really interesting things over the last day. I think, certainly, this group and others are probably already interested in asking whether there is verifiable data that would change their position.

Yesterday, Dr. Arnold I think gave a very interesting talk, very entertaining talk, and, clearly, very knowledgeable talk as the representative from CHADD. He stated very clearly that he just had the one single slide about CHADD. And I'm definitely not representing CHADD, but I did want to point out what's readily available on their National Resource Center on ADHD, which is -- the Web link is down below there.

Dietary treatments eliminate or take out one or more foods in someone's diet, for example, sugar, candy, food with red dye. The idea is that being sensitive to certain foods can cause symptoms of ADHD. Careful research, however, has not supported this treatment, and this is still readily available on the CHADD website.

So I think that gets to sort of the last points that we have, which are related to why are colors used. And the FDA yesterday in their presentation already presented this information about why colors are technologically justified. I'll just reiterate what's already been said.

Colors offset natural color loss due to light, air, temperature extremes, moisture, storage conditions. Essentially, what happens is natural color in foods fades during food processing. And I think what that means is that if you have a product that has a naturally red color and you expect it's going to be red, and then you go to the grocery store shelf and it's brown or it's orange or it's yellow, it doesn't look like the way it's supposed it's supposed to look,

and the consumer then is concerned. They say, "This thing is not safe to eat. It doesn't have the expected color appearance." We have very clear information from consumers that they expect foods are going to look a certain way. So one of the uses of colors is to offset that natural color loss during processing, during storage, et cetera.

Foods also have color added, whether we're talking about FD&C colors or the exempt from certification colors, to correct natural color variation, even in some cases from batch to batch. The raw materials that are used to make a processed food can actually have variation in color. And if you were to go to the grocery store and you were to see a jar of your favorite food that was bright green and the next one is a little bit gray, you're probably going to ask yourself what's going on here; there's clearly something wrong. And so that natural color variation is of great concern to consumers, and for us I think it's another reason why colors are important in foods.

In some cases, they enhance naturally occurring color, not in a way that's designed to

mislead the consumer, but in a way that's designed to appeal to the consumer preference. And then they add variety. They add variety and wholesome and nutritious foods. The way that they do that is in many cases to provide a colorful identity to foods that are otherwise colorless. In some cases, they add aesthetic appeal.

There are a few cases for both exempt colors and at least one of the FD&C colors where they actually absorb some of the sunlight and protect flavors and vitamins that could be affected and broken down by that sunlight. And I think, ultimately, they play sort of a critical role in how we taste and enjoy food, how we think about food as being palatable.

They have been used a long time, too, and this is just a graphic. When margarine was developed as an alternative to butter, there were practically wars fought about the ability to put color into margarine. Margarine is white. Butter, as I think most of you know, generally, is sort of pale yellow.

So there was a question. The dairy industry -- and there could be some representatives out there today -- really didn't want to have color added

into margarine because they said people aren't going to buy as much butter; they're going to start buying margarine. And, in fact, that's true. The addition of color to the white margarine gave the expected appearance that the consumer demanded, and it allowed margarine to become a suitable alternative, in the eyes of consumers, to butter.

So in a lot of ways, I would say society really has come to accept coloring not as sort of a fraudulent attempt to mislead the consumer, but as a permissible by FDA and others throughout the world and really useful signal of what the food is expected to taste like, how it's expected to perform.

I think, ultimately, colors definitely do make food more enjoyable. That's not a technological justification. I think that's a reality. And consumer studies I think have shown that consumers just won't buy foods with color variations from the norm. If things look too different, they're going to be nervous that it's safe and that it's not what they want and not what they expect.

So you could ask the question, and I think we

ask the question all the time, well, why do we still use FD&C colors. If we have all of these exempt from certification colors that are out there, why do we need FD&C colors? And I think what I would say offhand is natural colors are great. The market for natural colors is growing, not declining, by any means. The FD&C market I think is declining a little bit.

But there are still some technological limitations to the use of natural colors. There are certainly stability issues. Some of the applications in which colors are used, currently, we don't have a natural color that will really meet that specific demand due to the way that the specific product is processed.

In some cases, the range of colors is somewhat limited. We don't have a great palate, for instance, of natural colors that are nicely blue relative to Blue1 and Blue 2. And I think the other thing, too, is that we have limited resources. The natural colors are not in easy and available supply at this point. That said, research is continuing. R&D is constantly developing. As the market for natural colors grows,

and it's clearly growing, I think we will see more and more alternatives to FD&C colors.

So what's happening in Europe? Well, in Europe, all food additives are given labeling codes that are commonly referred to as E-numbers; so, E-102 or E-161B or E-122. They're referred to as E-numbers. Some people call them E-values. In fact, all food additives have that, whether we're talking about a color or an artificial sweetener or preservative or something.

So in many cases, colors were traditionally labeled in Europe not by a specific name, but by their E-number. Now, a manufacturer would have the option to do either one, but what we've seen is that in a lot of cases, the specific name was not used and that the E-number in fact was used.

I think over the years, that has caused some confusion and concern in Europe, particularly in the European consumer, about what is E-122, what is E-141, because they don't see that specific name. And the EU Parliament, I think, out of an expression of that concern that the E-number doesn't necessarily indicate

what the specific material is, has now required labeling, only I should point, for the Azo dyes, the six Azo dyes that were used in the Southampton study, that indicates that the dye, either listed as the E-number or the specific name, as is legally allowed, may have effects on activity and attention in children.

I should point out, there are a lot of issues, I think, related to the labeling as to whether it might be justified based on the scientific opinion of EFSA, but nonetheless, that is the situation now.

The question I think we would ask is, "Well, do U.S. labels need a warning label?" First of all, let me stress, again, I think it's our current position that there's no proven causality to hyperactivity. We think the studies are very interesting that have been done. We think that there is a lot of value in pursuing these issues further, to the extent possible, to developing good guidelines for doing these types of studies, but no proven causality at this point.

In the U.S., additionally, FD&C colors are already listed by name and not by the sort of vague E-number. So you can go to the grocery store, and if

it contains Red 40, it has to be on that label. If it contains Blue 1, it has to be on that label. If it's not on there, that's an illegal product.

I think ultimately what that means is, as with all food ingredients, if the consumers choose to not eat a specific ingredient because they have some concern, whether we're talking about FD&C Yellow Number 5, whether we're talking about soy lecithin, whether we're talking about an artificial sweetener, whether we're talking about consumers interested in reducing fat, salt, sugar from their diet, they can look on the label and they can make an informed product choice.

One of the, I think, examples here that would be relevant is carmine cochineal, and this, interestingly enough, was also the subject I think of a Center for Science and Public Interest citizens petition, I believe, that was filed back in, I want to say, 1998 or 1999. I'm a little unclear on the exact date. But this was based on the fact that there were anecdotal reports of people that had specific sensitivities -- whether it was allergenicity or not,

we're not really sure -- to the specific color additive carmine cochineal. This is an exempt from certification color, doesn't require specific labeling on the additive at the time. You would just have to say "artificial color added."

As a result of the review of the data, the ultimate conclusion from the U.S. FDA was that carmine cochineal should be labeled to give consumers that informed choice, not a warning label, but just to say carmine cochineal on the label.

I'll just say -- and my picture didn't come through down here. But colors are also used in other applications, and drug dispensing and consumption errors really are a significant health problem. Surveys of pharmacists and other dispensers have shown that color and shape are the most important attributes for patients when identifying medications, whether that's something that a parent gives to a child, whether that's something that a senior citizen takes to keep healthy.

What they've shown, or what I think has been clearly shown, is that colored tablets significantly

reduce medication errors. So the use of colors I think plays an important role not just in foods, but also in other applications, which I think, again, would add to the normal -- the normal follow-on question here would be, "Well, why not use natural colors? Why do we still use FD&C colors in those applications as well?"

I think the clear thing is that natural colors work great in a lot of drug applications, but there are some technological limitations related to the stability of natural colors, related to the limited resources, et cetera.

The shelf life of a lot of active pharmaceutical ingredients is still more than one year, while the shelf life of some of the natural colors is less than one year. So we have a somewhat limited palette of stable natural or exempt from certification colors that we can use currently. But, again, as with the general trend, I think, toward more natural, more exempt from certification color, research and development continues.

So, ultimately, I think we'd say there's a pretty strong and a very robust data set that supports

the safety of many synthetic or FD&C colors. And when I say many synthetic, what I really mean is the FD&C colors have a lot of data. Some of the colors that are not approved for use in the U.S., we haven't done those studies. Europe certainly is looking at them and generally is confirming that they're safe.

No proven causality for hyperactive behavior that we I think can clearly draw. The question about the use of mixtures in this testing I think is daunting. Assigning biological mechanism, I think is an interesting approach that should be pursued further.

We feel strongly that colors are useful additives that provide important and beneficial technical effects, and I think, ultimately, we think that colors are very clearly labeled already. The FD&C colors are already on the ingredient label, and this really already allows consumers to make informed choices. I think the market will ultimately decide whether we shift dramatically toward natural colors, whether FD&C colors over the long term have long-term market viability. But we think that the labeling as it is, is very sufficient.

This is my last slide. I provided a handout to the Food Advisory Committee this morning. There was some discussion yesterday about how much color is actually used, for instance, in cupcake icing. And we don't have cupcake icing data to provide to you this morning. What we provided to the committee this morning is, in fact, data from a chocolate candy coating. So this is a white chocolate in which some color has been added.

What I wanted to point out there is that to get that sort of deep pink color that's on the left side of that handout -- and that's the only one for which we have good data -- it was made using a mixture of Red Number 3 and Red Number 40. The application levels are pretty low, about .046 percent of the solution, which, in terms of total dye content, would only be about .01 percent.

As we calculated what that would mean, a .01 percent application level, if you were looking at, say, a cupcake icing, and we would suggest that maybe you would use about, let's say, 100 grams of that stuff or 100 mils of cupcake icing to frost a cupcake, we think

that that would be about 10 milligrams of intake of this dye mixture.

I think yesterday the interesting presentation from Ms. Edelkind suggested that you would really only use about three tablespoons of cupcake icing. I probably like a little bit more cupcake icing than others perhaps. So potentially, using her numbers, the intake would actually be more on the order of about 5.4 milligrams to develop this sort of deep pink color.

Now, let me stress, we think that's consistent with good manufacturing practice guidelines. That is the level of color that's needed to develop that deep pink color. Food companies and application specialists within those food companies, they're not going to use more than that if they don't have to. Colors are not an inexpensive food ingredient for food companies to use. They want to use as little as possible to achieve the desired technical effect.

I think the other thing to point out here, too, is that colors have sort of a saturating effect. So you can really only add colors up to a certain level, and once you get up to that level, if you

continue to add more color, it doesn't really add anything. The color essentially is saturated out.

So we think for this particular application, that sort of deep pink frosting level, we don't need 58 milligrams for good manufacturing practice. We need about 5 with the 3-tablespoon application level.

Thank you.

DR. ACUFF: Thank you very much, Dr. Taylor.

Okay. We have several questions from the committee, and Dr. Jones is first.

DR. JONES: Tim Jones. I have two questions. I guess the first is that, basically, for historical reasons, the FD&C colors are regulated and then the long list of others is not, and I guess in some respects, that decision is rather capricious. Contrary to public opinion, I think the label of being natural is not any guarantee of safety, and there are lots of natural substances that can kill you. So out of that long list of unregulated colors, are you aware of any studies, like these bookfuls that we're looking at, any studies of those substances to demonstrate that they are any safer?

DR. TAYLOR: Let me stress, these are regulated colors. So the distinction between FD&C or certified colors and exempt from certification colors doesn't necessarily mean that there needs to be less sufficient safety data supplied and that the FDA has reviewed. In some cases, because of their long history of use -- and, for instance, let's look at fruit juice or vegetable juice. These are commonly consumed foods. Things like saffron, to some extent, or the carotenes, beta-carotenes or beta-apo-8 carotenal, these are present in carrots, for instance, so they don't necessarily require the same level of toxicology testing that's been done, but they do have a lot of data.

Not all of them have as much, and I think one of the interesting things that we're seeing -- because the European Food Safety Authority is not just focusing on what would be considered synthetic colors; they're looking at all colors that are used in Europe, including a lot of these, and they are asking some questions. They're saying, "We're pretty comfortable with the data set for the FD&C or the so-called

synthetic colors, but we do think that there could be some data gaps with some of these colors, as well," and we're addressing those.

I think your point is very well taken in that while there's a lot of interest in natural -- and I'm not just saying natural colors, but natural in general. I think if you look in the clothing industry, people are wearing cotton now versus polyester 15-20 years ago. So there's just a general push, I think, toward natural, and that's reflected not only in the significant increase, I think, in the use of exempt from certification colors, but throughout the entire food supply.

DR. JONES: My second question is you've made a good argument that color is important, but I think one of our readings said that Whole Foods and Trader Joe's don't carry anything with those FD&C colors, and you don't walk into a place like that and think, "Woohoo, this is a particularly bland environment."

So with all of those choices, in relative terms, this other handful, how important are they really?

DR. TAYLOR: It's a good question, and I think the simple answer is we don't have great volume data. I think one of the limitations in terms of assessing overall color exposure is that we really don't have great data on these exempt from certification colors.

What we do know is if we talk to members of the color industry or members of the food industry and we say, "How easy is it for you to replace a yellow color with riboflavin," the first common answer is, "We can't get enough of that material right now." The use of FD&C colors throughout the world is, I think, still very high. And so there aren't sort of simple replacements that can be done primarily based on limited resources, and as I said earlier, also based on limited technological applications at this point. So I think they still play a pretty important role overall.

We do know that processed foods throughout the world, their use, their sales are increasing, particularly in developing countries, in Asia, in India, in China. A lot of that is related I think to the increased spending power that the consumers have in those countries and their interest in having processed

foods versus, in many cases, other fresh foods.

DR. ACUFF: Dr. Gray?

DR. GRAY: Thank you, Dr. Taylor. I have a question that goes to your biochemical knowledge, so I'm hoping you can help me out.

You made a very, very interesting observation about the ability of these molecules to even get into the brain, and it actually reminded me of how I teach my students about the blood-brain barrier and its discovery by the German biochemist, Caryl Ehrlich, who also won the Nobel prize, who injected a dye -- not one of the ones we're talking about, but trypan blue -- into an animal's blood stream, realized that it stained the whole animal, except for its brain and its spinal cord.

DR. TAYLOR: Yes.

DR. GRAY: So that's a very important point. And what I'd like to know is, from the kinds of studies that you talked about, if we have a better idea of the distribution of both these artificial food colors and potentially some of these exempt colors, do they reach the brain, which ones reach the brain, and how much of

them reaches the brain?

DR. TAYLOR: I would say our knowledge is limited. I'd love to be able to say we have incredibly extensive studies that have looked at transport, that have looked at ultimate amounts within the brain. The data that we have is primarily based on the toxicology studies that have been done and based on the extensive histopathology after necropsy.

What we would assume, as I think you're alluding to, is that if the dye is pervasive, if it's commonly absorbed, if it's distributed throughout the body, because it's colored, you're going to see it, and we haven't seen that, or I should say the studies have not shown that.

We don't see any significant amounts of color in the brains of any of the animals that have been done, with the single exception, I will point out again, for Blue 1. I don't have a great chemical basis to explain why Blue 1 seems to have a little bit different transport properties, but we do know that Blue 1 has some capability of crossing the blood-brain barrier.

It's actually an interesting story. I think it was about, I don't know, a year or two ago, I came into work one day and there were probably 100 e-mails in my in-box. And every single one of them had this picture of this blue mouse. And there's some research that's out there that suggests that Blue 1 may help, in some way, in treating spinal cord injuries, because it does have, apparently, the capability to get into the nervous system. Beyond that, I think the data that we have suggests that there is no significant distribution.

I think yesterday there was a slide that was presented that showed this blue colon, which looked pretty nasty to me. But I think it's important to keep in mind that was a critically ill, a terminally ill patient that was being given Blue 1 as part of a liquid diet that was given through enteral feeding. And what they were specifically doing there was they were trying to assess whether the patient was keeping the liquid down. So I think this is called aspirational detection.

So it's a way, if the blue dye obviously comes

back up and you see it, you know that the patient hasn't been able to keep the food in their digestive system.

We also know that that specific patient had, I think, diabetic nephropathy. And so I think it suggests that the indications that were given with that particular colon may not necessarily be a good indication of the distribution throughout the entire body.

DR. GRAY: And one quick follow-up. Am I right in recalling that Blue 1 was not in the Southampton study?

DR. TAYLOR: Blue 1 was not in -- Blue 1 is not an Azo dye. It's a fundamentally different type of pigment relative to Red 40, to Yellow 5 and Yellow 6.

DR. ACUFF: Dr. Voorhees?

DR. VOORHEES: Thank you. Let me start by asking you -- so you're aware of the background document of the Food Advisory Committee by the FDA. Could I ask you, are you aware of why the ADI calculations that the FDA used in their table are all based on two-year rodent bioassays?

You presented us with a lot of safety studies that have been done, but they don't seem to have been used in the determination of the noaels, as far as the FDA is concerned.

DR. TAYLOR: Yes.

DR. VOORHEES: And why is that?

DR. TAYLOR: To the best of my knowledge, that's related to the fact that the two-year bioassay noaels, in general, would be more conservative or they were the most conservative. I think nowadays, most people would probably suggest that 90-day toxicity study, noael values would likely be used to establish initial noaels. But that's my understanding of why they were used.

DR. VOORHEES: So could I ask you, why is it that in all those safety studies, there is -- we're here to discuss the issue of whether or not food additives produce effects on -- affect behavior.

Not one of the studies that you listed among the safety studies is what is commonly referred to as a DNT study, and that's developmental neurotoxicity study. So, in fact, it isn't clear to me that you have

preclinical data that speak to the issue, which is the subject of this conference.

So I would ask you, do you think that the data that's available really speaks to the issue under consideration?

DR. TAYLOR: Well, I think that developmental data like that is definitely not something that we have within this jacket of studies that were provided to us or that the FDA guided. I think that the data that's been presented within the FDA report, primarily these types of behavioral studies, may well be looking at different endpoints than the DNT type studies. I think it is an interesting question as to whether some of those types of studies could be done or should be done.

DR. VOORHEES: Well, if you were going to do a preclinical study that looked at developmental behavioral effects, I'm just raising the issue with you, isn't that the study design that would be most appropriate to addressing this issue. That's the kind of safety study done by other federal regulatory agencies in order to determine effects on brain and behavioral development.

DR. TAYLOR: I guess I would say that's probably a little bit outside of my expertise area, so I don't know if I can cogently comment on that.

DR. VOORHEES: Okay. Let me ask you the other question. So you presented data or you referred to data, preliminary data that says that the food color that you've looked at doesn't cross the blood-brain barrier.

So what is the embryonic blood-brain barrier?

DR. TAYLOR: It's definitely not nearly as developed as the adult blood-brain barrier.

DR. VOORHEES: There really isn't one.

DR. TAYLOR: Yes.

DR. VOORHEES: What about the fetal blood-brain barrier?

DR. TAYLOR: I think there is very little evidence that there is a clear blood-brain barrier.

DR. VOORHEES: What about the infant blood-brain barrier?

DR. TAYLOR: I think that's when the blood-brain barrier begins to develop.

DR. VOORHEES: True, but it's in an incomplete

state of development.

DR. TAYLOR: Yes.

DR. VOORHEES: What about childhood blood-brain barrier?

DR. TAYLOR: I think that's also where the blood-brain barrier sort of continues to develop. But I would note that, to my limited knowledge, there are definite differences between the adult blood-brain barrier and the child blood-brain barrier. And so there could be potential differences in transport, which I think is why, when these animal studies were done and when they looked at distribution, for instance, in the brain, they didn't look at adult rats; they looked at young rats. And, again, certainly, we're looking at animals versus humans, so there are some caveats there. But I think that was the attempt.

DR. VOORHEES: So are you saying that the particular food additive that you refer to, whichever one it is, they looked at blood-brain barrier transfer in early developing brain?

DR. TAYLOR: I think to clarify, the study that was done was part of the toxicity study. So

ultimately what they did was not look at specific transfer or transport through the blood-brain barrier. They looked for the presence of the dye or its metabolites within the brain, making the assumption that if it crossed the blood-brain barrier, that you would expect to see the dye.

DR. VOORHEES: But was that in an adult rodent?

DR. TAYLOR: That was done in adults, but it was also done in developing or young rodents.

DR. VOORHEES: So we were not provided with that data, so that's a difficult situation.

So you are aware that there is a presidential executive order that requires all federal regulatory agencies to take children's health into account apart from other kinds of safety assessments.

DR. TAYLOR: Certainly, yes.

DR. VOORHEES: And do you feel that the data set that you summarized, that have been collected on the food additives, adequately addressed that particular aspect of safety determination?

DR. TAYLOR: Well, I think that -- it's a good

question. I think if we look at not just the safety data here, but we look at all of the data that's been presented over the last couple of days, I think there are still a lot of questions that need to be addressed. And I think some of those questions may be additional behavioral studies. I think some of those questions could be additional biochemical or biological mechanism studies.

DR. VOORHEES: So what would trigger the manufacturers to decide that it would be appropriate to undertake developmental neurotoxicity or neurobehavioral studies in order to help provide added information to determine that the ADI calculations are not, in fact, shifted for developing organisms? You've had those data sets for some years.

DR. TAYLOR: Yes. It's an interesting question, and I think – certainly within the U.S. framework, I think that would be with the guidance from the FDA. The most recent safety evaluations, as I said, were done by the European Food Safety Authority. We're a global industry; we're not just a U.S. industry. So we have responsibilities to those

regulatory authorities as well.

Within all of their opinions, they do specific exposure assessments and specific questions related to children, relating to whether there are significant differences in take or potential toxicologic outcomes for those children relative to adults.

As a result of those studies -- I'm sorry. As a result of those opinions, if there are requests for additional developmental or toxicity data, that's something that we would take on.

What we haven't seen from any of the EFSA opinions that have come out has been that level of concern. And I think I would say that -- I think it's fair to say that the European Food Safety Authority is as similarly concerned about children's health as is the U.S.

DR. VOORHEES: So in this document that's been prepared for background by the FDA -- so when they try to look at a scenario, which they point out has been endorsed by the World Health Organization, they use this system of taking the poundage produced and making an assumption that it's not distributed evenly across

the entire population. But to look at perhaps a subset of high consumption, they use this 10 percent.

If you look at the ADIs compared to the EDIs, there are three of the dyes where the values under this calculation, in the case of the 30-kilogram child, are, in fact, very close.

DR. TAYLOR: Yes.

DR. VOORHEES: These reach less than 5 percent within the presumed safety margin, given the assumptions of the safety margins that the FDA uses to establish safety.

So does that concern you that these are so close?

DR. TAYLOR: Well, I think it's important to recognize also that both the estimated daily intakes, as done by the FDA, and also those done by JECFA, make this significant 10 percent eaters only estimate.

The 10 percent eaters only estimate that's done by JECFA I think is recognized as a very conservative approach, particularly for food additives, including color additives, that we know are used pervasively throughout the food system.

There are examples, certainly, of other types of food additives. You could look, for instance, at flavoring substances, for which we know that that 10 percent eaters only estimation is probably fairly realistic, because there only are specific populations that eat, let's say, pesto on a regular basis, or that eat a specific type of yogurt with a blueberry flavor. Some people are just averse to those types of things.

So the eaters only assumptions there I think are good conservative assumptions, but probably for food additives that are pretty pervasive throughout the food supply here in the U.S. and certainly throughout the world, I think it's a pretty conservative assumption.

It doesn't mean we're not concerned about it, but I think we also sort of accept the conservativeness of that approach. And when we couple that to what we know about the use of certification in the U.S. versus the actual amount that enters into the food supply -- and while I don't have exact data, I think that would be something that would be really interesting to perhaps refine those EDI numbers.

DR. VOORHEES: But the FDA in fact used only 73 percent as entering the food supply, so they've already made an effort to make an adjustment for that.

The other thing, that we've been presented with data from FDA and other sources, that the annual volume production of food additives has been steadily increasing. So if these three are getting close to the 10 percent margin and the production of these is rising progressively, there is going to come a point where those estimates cross the threshold.

Would the crossing of the threshold by these calculations then produce an increase in your level of concern about conducting further preclinical safety assessments?

DR. TAYLOR: Absolutely. I think with any sort of work, as the exposures are refined or increased, if there is some concern about the value versus the acceptable daily intake, then that is generally the trigger. JECFA, when they evaluate flavoring substances, color additives, artificial sweeteners, anything, if they believe that you're getting too close to the acceptable daily intake, then

they try and figure out what is the most appropriate net study to do to ensure that your material is still safe.

I think I should stress, and I'm sure many of you are aware, that when these acceptable daily intakes are established, there's still a significant margin of safety between the ADI and the EDI. So the acceptable daily intake is established based on some relevant noael value that would still provide sort of a safety factor of anywhere between 100 and 10,000, depending on the specific study and how much concern JECFA had about it.

DR. VOORHEES: These are all based on 100.

DR. TAYLOR: Okay.

DR. VOORHEES: That's what the FDA says. So they're not -- I mean, they're fairly standard, but they're not highly conservative. And I don't believe they include an additional margin for development. And you know that in other regulatory agencies, there's an additional risk level, another 10-fold, I believe, that's put in for developmental exposure, which is not present here. And if you change this safety margin

from 100 to 1,000, these values would all be over.

DR. TAYLOR: Yes. Yes. Like I said, I think it would be valuable at that point also to then refine the exposure to see what is the more realistic assumption related to exposure.

DR. VOORHEES: And since you don't have developmental neuro studies, for all you know, the no effect or no adverse effect level might change.

In a recent review by the Environmental Protection Agency of their development neurotoxicity studies on the agents that they reviewed, they found that developmental studies set the no adverse effect level and the point of departure for risk assessment in many cases.

So there is a reasonable scientific basis for thinking that developing organisms, and this has been developing over the last 20-30 years -- that the developing brain is in fact more susceptible to external influences than is the adult. It seems like it's a concern that there is less data available on these particular products that address those particular concerns.

DR. TAYLOR: I think it's a valid point. I think, ultimately, if anybody, whether we're talking about the requests that have been made from EFSA, whether they would come from JECFA, or certainly from the U.S. FDA, the industry has a responsibility to respond to ensure that these products are safe.

DR. ACUFF: Dr. Winter?

DR. WINTER: My question is related to the calculations of exposure. It seems as though most of the exposure estimates seem to be pretty crude looking at disappearance data of certified volumes and poundage of the ingredient.

Sort from my perspective, I almost like to look at it from the other side. Is it possible, in your opinion, to be able to build a relatively robust system of exposure estimates to these dyes by considering levels of dyes in individual foods, then combining that with data such as NHANES to figure out how much of these various food items are being consumed, which would avoid having to make these 10 percent assessments and would also then give us a probabilistic assessment so we can look at the top

10 percent of consumers and also look at different age groups.

Is that something that you see as possible?

DR. TAYLOR: Yes. Actually, I think that's a really interesting question. There are a couple of things that have gone on over the last, let's say, 5 to 10 years related to this. One is there is an effort within the European Union -- it's a project called the FACET project, which is an attempt to develop a new exposure technique that would allow for the estimation based on presence in food as measured in the final food product, based on national consumption data, the NHANES type data, based on input from experts from the industry, from other parts of the world with expertise, to devise very refined exposure estimates.

This project, I think, is based in Ireland at -- I want to say Dublin University, College Dublin. Mike Gibney I believe is the name of the person that's in charge of this project. And I think it's a really interesting project. It's going to have some limitations. The data is not going to be perfect. They can't look at everything. I think they're looking

at a small number of food colors, but I don't know for certain which of those. We haven't been requested to provide any data from sort of the U.S. side. I can't verify for certain, but I can certainly find out whether some of our European partners have been.

So I think that's one thing, and I think that we will see some refined exposure assessments based just on that alone. And I ultimately think that those types of exposure assessments are going to be really important going forward, to move away from sort of the crude how much goes into the food supply, because, as I said, we know a lot that's certified is not being put into the U.S. food supply.

I think the other pieces of data that we have related to this are really what's been published, and a lot of this work, again, comes primarily from Europe. We've seen some exposure assessments done in India. We've seen some in Korea. I think that's about it. I'm sorry, and also certainly one that was done in Australia.

A lot of the most refined exposure assessments that were done I believe were probably done in England,

the U.K. They have a very, very good consumption database that covers a very broad swath of the Irish population, all age groups, a good number of people. So they have a pretty good idea of how much food is consumed and which types of food on a daily basis in the Irish population.

A lot of that work I think was published by David Tennant, who is also an expert in exposure and has done a lot of work. Generally, what he's seen -- and I think he's looked at beverages, in particular. Generally, what he's seen is that the levels of colors in these products relative to the ADI is actually very low. It was I would say comforting data for us. We weren't involved in that work whatsoever. It was an academic project. To be honest, we didn't really know about it until the paper was published. But we generally see that that's the case.

Now, in other parts of the world, I should point out, we do see the potential exceedance of the ADIs. There is a study that was published in India, I think where they looked at a small population in maybe Hyderabad, something like that -- I'd have to go back

and look -- and the paper there suggested that of the six colors that they looked at, there was one that exceeded the ADI. I'd have to go back and look at the details.

But this type of exposure work is really ongoing, and part of it is actual testing of the final food products. We've given you some of that data here this morning. Some of it is based on consumption data. And I think it's ultimately pointed to the fact that we should be able to refine these exposure estimates, and I think that's a valuable exercise as we start to talk about certainly child development and the child's intake of these food colors.

DR. WINTER: Just one quick follow-up, if I can. So all these colors are required to be labeled in the United States. The FD&C colors are required to show up on the label, therefore, there should be some indication of how much of those are actually in, say, a processed food product.

Is that something that is proprietary information or is there such variability that it would make it difficult to make those estimates?

DR. TAYLOR: It's primarily proprietary information, I would say. What we know in the color industry is most of the color companies have what we would refer to as sort of application specialists or development specialists, and these are the people within these companies that might get a brief from a food company to help them develop a product that has an orange color. And that application specialist would figure out what might be the most appropriate level or strength of color to use, potentially which color, whether it would be an FD&C color or an exempt from certification color. Ultimately, the food company may make some adjustments there.

So we don't have that specific information, but what we could do, I think, is we could survey the industry. We could ask, "In the best estimate of your application specialist, how would you anticipate these colors would be used in confectionary products, in baked goods? What are the different subcategories within this larger baked goods category would you expect the colors would be used?"

That type of information, I should say, is

being provided, to some extent, to the European Food Safety Authority and to the directorate general for Sanitary and Health Affairs in Europe, DG SANCO, to try and revise maximum permitted levels in Europe, to try and understand how the food industry generally is using these products.

DR. WINTER: Thank you.

DR. ACUFF: Okay. We're already over time, but we have four additional speakers wanting to ask questions, and these are important questions. So I'd just like for you to keep in mind that we're already over time and make your questions and responses as quickly as possible.

The next one is Mr. Waldrop.

MR. WALDROP: Thank you. Chris Waldrop. First of all, this handout I think is a little misleading. No one is talking about kids eating nine pounds of frosting, although there may be some kids out there that want to try that. But you say one cupcake has 10 milligrams of dye. I think when you start factoring in other foods that may have different levels of dyes, then you may start getting up closer to that

average daily intake. And so I just wanted to say that.

Second, you talked about sort of consumer expectations of foods and why dyes are being used. And one of the things you said was consumers expect foods to look a certain way. And that may be true for some foods, but it's probably not true for things like yogurt. When you ask consumers what color yogurt is, I don't think they're going to say it's bright blue and bright pink, which is what I've seen my nieces eat in terms of yogurt.

Then you said the consumers won't buy foods different from the norm. But, again, I think in some instances, the norm has been shifted, because almost all kids' cereals are brightly colored, and I think that's probably because kids are attracted to bright colors, and if you market kid's cereals with those bright colors, they tend to buy them. So the norm may be brown cereals, but that's been shifted in certain segments of food categories.

Then you said in terms of additives being on the label, consumers can make informed choices. That

seems to be a bit different statement than what you said in terms of consumers won't buy foods from the norm. If consumers can make informed choices, but yet you're saying that they won't buy foods that are shifted from the norm, that means consumers are going to be buying grayer colored products instead of green colored products. I just think it's a little bit -- you're kind of making two different arguments there.

DR. TAYLOR: I think the important thing to keep in mind here is when we talk about labeling, we're primarily talking about labeling that's for the general population. It's for everybody. If you're a specific consumer who believes that you have a unique intolerance to any food additive, you're going to become part of sort of a special subgroup, and that special subgroup is going to be particularly attuned to the presence of any food ingredient.

So I think the general consumer preference is for foods that meet their expectations, both flavor, color, et cetera, but there are certainly specific subgroups that look at that label very closely. And if

that color is on that label or that other food additive of some type is on that label, they're not going to buy it, even if it ultimately means that they end up buying a product that doesn't have the expected color or the expected flavor.

MR. WALDROP: And I would also say if consumers are worried about, in this instance, attention deficit disorder or hyperactivity and they're worried about food dyes, not all consumers have made that link. I mean, there are certainly informed consumers that are trying to make that link, but not all consumers are. And so they may not know that this particular thing may have a possible association with food dyes. So just the fact that it's on the ingredient label may not be enough.

DR. TAYLOR: Well, I think, also, though, there is I think increasing awareness not just for ADHD effects, but just across the board. What is the food we eat? What are the health effects of that food we eat?

So I think the consumers are becoming better educated over time, and I think our members and

certainly the food industry wants to push that forward. I think that's a good thing. I think we all feel that that's a really good thing. I just think ultimately we don't necessarily know that a specific warning label that would apply to all colors, based on data that is intriguing but potentially incomplete, is a good solution at this point.

DR. ACUFF: Dr. Vugia?

DR. VUGIA: Thank you. Duc Vugia. I have two brief questions. You've talked a lot about the association of having a lot -- or at least there have been many pharmacokinetic studies and that there are a lot of data on it, but there were no specific data shown.

My question on this is, do you know how long after ingestion of the certified colors does it peak in the body, whether an animal or human, and how long does it stay in the body?

DR. TAYLOR: And I apologize. I don't have that data at hand. I probably have it on my laptop, and I could look it up and try and provide it to you here shortly. We know that the lifetime is very short

in the body, but I'd have to go back and I'd have to look to see what the sort of Tmax or the Cmax were. I don't have it in the back of my head.

DR. VUGIA: Well, can you give a ballpark, like is it hours or days?

DR. TAYLOR: I think it's less than hours, actually. It's pretty short.

DR. VUGIA: Okay. The next question is about you mentioned and criticized or gave comments on the Stevenson study, studies from the Isle of Wight. Given that this study came out in 2007 in Europe, there is a lot of concern there, obviously, and reaction.

Do you know whether the International Association of Color Manufacturers or the European counterparts have actually considered or implemented studies looking at clarifying some of this issue resulting from the study; for example, looking at combination of colors with and without sodium benzoate, for example, in animals, at the very least?

DR. TAYLOR: I can say as soon as this study came out back in 2007, we had a meeting, and we said what do we do, what's the next good step, from all

sorts of perspectives, because we knew that there would be a lot of interest in this study because of the results.

I think the ultimate conclusion we came to is what is the best way to do this study. Do we try and replicate the results from Stevenson? Do we try and use some different method that might be slightly improved? How do we know that the methods that we would try would be acceptable to the international community, to experts within behavioral development?

So I think in a lot of ways, we've kind of relied on the opinions of, for instance, the EFSA experts to help guide us to know whether there are some additional specific requests.

To be frank, I expected that when the EFSA opinion came out related to the Southampton study, that they would say, "Here are four follow-on things that we want from the industry to make sure that we're comfortable with the safety of these colors," and we didn't get that. I guess it was pretty surprising, because I think we would view them as a very conservative body in terms of safety evaluation.

So I think ultimately what we would really like to see is we would like to see good ways to do these types of studies, good guidelines, ways to validate these studies and to ensure reproducibility.

There were some questions yesterday about whether they had been replicated between the Isle of Wight and the Southampton study. I don't know if they really have, to be sure, because I'm not positive that the global hyperactivity audit was used in the same way in the Southampton study that it was in the Isle of Wight study.

DR. VUGIA: I just want to clarify. So what you're saying is that despite the concern of the industry over this study, they have not taken any action to actually try the study even in animals.

DR. TAYLOR: We have not. What we've done is we've gone back and we've looked at the data that we had. Again, we asked are there relevant issues related to crossing the blood-brain barrier; are there any potential biological mechanisms that we can relate this back to.

But in terms of doing additional animal

studies, at this point, we haven't done those. I think we'd be interested in doing them if we can figure out the best studies to do, but I think that's challenging.

DR. VUGIA: Thank you.

DR. ACUFF: Ms. Lefferts?

MS. LEFFERTS: Lisa Lefferts. I'm the consumer representative on the committee.

Your first slide said that you represent the interests of the industry by demonstrating safety. And several other speakers have asked you this question, but I just want to really nail it down. All these studies that we are assessing, has your industry provided any funding for any of them or any other studies that address this issue before the committee?

DR. TAYLOR: I think it's a great question, because there are definitely criticisms about industry-sponsored studies and whether a study that the industry would support would be reviewed favorably by an international body, for instance, and we haven't. So these are independent studies.

MS. LEFFERTS: There are ways, of course, to fund a study and have it retain its independence. But

I take your point. That was my question.

DR. TAYLOR: To clarify, though, just to clarify, the safety studies in terms of the toxicology work that was done, those were industry-sponsored studies to put these things through the color added petition process. The only way -- the only support that would be garnered to do such a study would be for an interested party, the industry or a specific member of the industry to carry out those studies. But when they were done, they were done using sort of very strict guidelines. They were done with substantial consultation from the FDA, who had very strict control over how the studies were done.

MS. LEFFERTS: A couple other speakers have mentioned this, also. You're saying that you do have blood-brain barrier studies, pharmacokinetic and metabolism studies. Are those data published?

DR. TAYLOR: Just to clarify, we don't have blood-brain barrier data. What we have is clinical histopathology data, data related to after the animals are sacrificed in toxicity studies, the presence of whether these dyes are in the brain, which would be an

initial indication, either in young rats or adult rats, for whether the dye was getting into the brain.

So we have that data. All of that data is in the public record. It's either been published in papers, or if it hasn't been published in papers, it's within the sort of larger jacket of data that was submitted to the FDA.

MS. LEFFERTS: Also, does your industry represent both certified color manufacturers as well as natural?

DR. TAYLOR: Yes, absolutely. We're both certified and I guess I would say exempt from certification colors.

MS. LEFFERTS: Okay. You mentioned that consumers expect foods to look a certain way. The committee received, if I counted right, 7,932 comments from consumers. Pretty much all except one, that was sent in by a group that was supported by food and agricultural interests, expressed a great deal of concern about the effects of food additives on colors. And these were comments by parents, teachers, nutritionists, doctors telling, their stories, how they

are often -- they were not aware that this could even be an issue. And now that they've figured it out, they want everyone to know and they want FDA to do something about it, basically.

So I think merely labeling the ingredients, as the other consumer representative on the committee has mentioned, is losing a lot of consumers. Consumers can make informed choices, but they need to be informed.

Your point about Azo dyes I found interesting. Other agencies are looking at mixtures of a similar class or similar mode of action. So that was an interesting point you made about Azo dyes.

DR. TAYLOR: I think I would say, generally, the testing of mixtures, specifically in toxicology, is a really challenging subject, and I think it can be very difficult to draw clear conclusions from the testing of mixtures. But, nonetheless, I do think it's very intriguing to look sort of at a more chemical or biochemical approach related to Azo dyes or to any of these chemical classes.

MS. LEFFERTS: What would prompt your industry to fund studies that would help address this issue?

You mentioned that in other countries, the ADI has been exceeded. This hypothesis has been around for many, many years. Consumers are very concerned.

Would it really require a government action, a request or other regulatory action?

DR. TAYLOR: I think one of the principal things here is that we'd love to see a good way to do these studies that would be acceptable internationally. And as I said, studies that are sponsored by the industry are often not well received because there is this suspicion or there is this concern that the way the studies are designed, it's to elicit a desire or no effect. And so I think a good independently designed study and potentially independently conducted study is something that would be of value for everybody, including the color industry.

This is not a subject that we're happy to have come up every 20 years and discuss. If there are real effects here, I think it's important that we see them. If there aren't real effects here, I think we'd like to try and ease the consumer concern.

DR. ACUFF: Okay. Ms. Menke-Schaenzer and

then Dr. Castellanos, and then we have to move on.

MS. MENKE-SCHAENZER: Dr. Taylor, early in your presentation, you talked about JECFA and that they're currently reviewing the safety of colors and there are results expected out in June and July.

DR. TAYLOR: Yes.

MS. MENKE-SCHAENZER: Can you share with us which colors they're looking at --

DR. TAYLOR: Sure.

MS. MENKE-SCHAENZER: -- and if you have any understanding of an early read?

DR. TAYLOR: I'm sorry. An early?

MS. MENKE-SCHAENZER: Early read of the results.

DR. TAYLOR: Okay. It's a good question. So the way this is worked is as the European Food Safety Authority has been carrying out their reevaluations, if they had changed the acceptable daily intakes in Europe, what they have now done is they've gone to JECFA and requested that JECFA reevaluate their earlier results.

As I said, a lot of the changes -- in fact,

all of the changes in the acceptable daily intakes in Europe that have happened have happened on the basis of reevaluations of existing data, where the no observed adverse effect levels that were previously noted have been changed.

The three colors in particular that are being looked at in this particular JECFA calendar year are sunset yellow, which would be FD&C Yellow Number 6, when certified; it's quinoline yellow, which is a color that's not allowed for use in the U.S.; and, Ponceau 4R.

Both quinoline yellow and Ponceau 4R -- I might be wrong, I'd have to go back and double check. But quinoline yellow, the acceptable daily intake was significantly changed, I think by a factor of maybe 10 or 15. For Ponceau 4R, I think the acceptable daily intake was changed by about a factor of 4. And sunset yellow is an interesting one because the acceptable daily intake hasn't been permanently changed. What they've done is they've established a temporary ADI, and they've asked the industry to do an additional 28-day study.

The specific concern there was some data from an Indian study that was done not according to any sort of standard OECD guideline. It wasn't a GLP study. We don't necessarily even know that the material that they tested was sunset yellow, because they don't have any records. But they published a paper that suggested that there were changes in sperm motility, I believe. So EFSA has asked us to confirm that this material that they have looked at previously doesn't show those types of effects.

JECFA this year -- to be honest, I don't have a good read on how JECFA is going to look at these colors and whether they'll agree with the European Food Safety Authority and change the ADIs. One of the challenges I think there is that we don't really have control over the data. We didn't submit any data for quinoline yellow and Ponceau 4R. We didn't sponsor those studies. We don't actually have the original study reports in our files, so there's really nothing for us to provide to them.

For sunset yellow, we've let JECFA know that we're carrying out this additional 28-day study. It's

possible, on the basis of that, if the final reports are not ready, JECFA may hold the evaluation of that for a year or they may complete it and establish another temporary ADI and also make a request for data, knowing that the data will be coming for the 2012 meeting. But that's my -- this is my personal view.

DR. ACUFF: Dr. Castellanos?

DR. CASTELLANOS: Thank you. A couple of areas. One, you made several comments about the Southampton study that you mentioned reflected others' judgments. And it seems -- well, one is first a correction of the way you characterized it.

As you said, they didn't record data during weeks 1, 3 and 5 placebo periods. It's true that they were receiving placebo during those periods, but there was a double-blind placebo phase during which they did collect data, and one of the challenges of doing this work, as was intimated by Dr. Stevenson, is the subject burden. This continuous performance task is absolutely deadly boring, and to have added three more of those sessions in order to get a bit more data would have produced an even greater time kind of effect.

But then you also mentioned that there were certain undefined terms in terms of when the additives were taken, when during the week the measurements were obtained, the fact that body weight wasn't factored in for each of these kids.

It seems to me, and I'd like your opinion on this, that all of those are the sorts of experimental error factors, in a sense, that decrease the signal that one might detect. In general, those are the kinds of things that produce more of a type II error; in other words, that you're likely to diminish the effect that you observe, greater variation of the time of day, et cetera.

Obviously, it would be great if this could be time-locked and we knew exactly the kinetics and all of these measurements were done to precise point of maximum exposure, et cetera, but that wasn't the case; it's not doable in a kind of naturalistic design.

So would you agree that those are the sorts of experimental factors that actually would diminish the magnitude of the effect?

DR. TAYLOR: Well, I'd have to say, again, I'm

definitely not an expert in this area, so it's difficult for me to say that. I think our concerns about the lack of data within the placebo phase wouldn't necessarily suggest that you would get a larger signal, because you might see additional inter-individual variability that would change the placebo effect in those weeks 1, 3 and 5.

DR. CASTELLANOS: I'm not following.

DR. TAYLOR: That's probably my ignorance. I apologize.

The other effects, the temporal effects, I think it would be very, very important to look at this data. And I understand and recognize certainly the challenges there. It is very difficult, I think, to do these studies.

But the third issue I think related to body weights, and I think possibly also related to volume, and I could be wrong here, as well. But it was my understanding that all children were given essentially the same volume and they were given the same amounts.

If children are given very large amounts of a fruit juice mixture, that could contain sodium

benzoate, that could contain colors. If it's a smaller child versus a smaller child versus a larger child, I think that could have effects either way. So I don't necessarily know that it could exacerbate.

DR. CASTELLANOS: Well, that makes an assumption that there's a fairly steep dose-response curve. One of the things that we've heard is that there's very little data on dose-response. There was a suggestion by one of the advocates yesterday that if we look at the data from a certain perspective, it appears that there's a dose-response relationship present. We can't really evaluate that fully. But there seems to be a fairly flat threshold within the range in which the studies have typically worked. So, theoretically, you may be reporting -- I mean, it's true that that might be the case, but the data that we are looking at doesn't support that there's likely to be a huge swing related to that in this part of the range.

DR. TAYLOR: I think in the absence of actual data, you could be right. There may not be a very steep dose-response. We just don't know. I think it's also obviously difficult to try and establish dose-

response using several different studies that used a different number of subjects, that used different mixes potentially of colors. There's just a lot of uncertainties there. So I think developing sort of a dose-response curve on that basis is challenging.

DR. CASTELLANOS: Clarification. You stated that you agreed or acknowledged that a behavior was amended in that trial, and that's not a usage that I'm familiar with. What did you mean by amended behavior?

DR. TAYLOR: Well, I think I would say, just to clarify, affected.

DR. CASTELLANOS: Affected?

DR. TAYLOR: Yes. I think that's reasonable. I think the one thing -- and we heard yesterday I think from Dr. Stevenson, in his very nice presentation, that in his view, this is a noticeable behavior change. But I think it's challenging -- and this was the words from EFSA more than myself. It's challenging to know what the real significance of that effect is in terms of downstream.

DR. CASTELLANOS: The argument that's being made is that a two-point change in blood pressure is

unlikely to be detected certainly by anyone subjectively or even by a physician who is making those sorts of measurements. But if we're able to shift the population mean blood pressure by two points, that has large significance in terms of the population health issues. And so that's I think is one of the questions that we have to deal with is in terms of our understanding of materiality.

But let me shift over to blood-brain barrier, because that's of great relevance to this question of mechanism that we've been struggling with, and a couple of things.

One is that you've mentioned that as part of the toxicology work, the neuropathology involves certainly at least a gross examination of the brain to see whether or not there's obvious dye present. But it sounds as if those evaluations were not made with the intent of understanding whether the blood-brain barrier was intact, to what extent it was breached, et cetera. It was more of an incidental gross notation rather than anything that we should take as compelling evidence of a lack of access to the brain compartment.

It doesn't sound like the development work -- we haven't heard anything about that other than your claim or your assertion that these young animals were also, in some cases, exposed. But do we know -- my assumption, and I guess I'd like to be corrected if it's wrong, is that those data are by no means compelling.

DR. TAYLOR: I think the data is definitely incomplete. You're exactly right. This is a gross examination in those cases where no apparent adverse effects were seen, and none were in any of these studies, where there was no obvious presence of dye or any of the metabolites within these gross examinations. There was no additional microscopic examination that was done.

DR. CASTELLANOS: Now, one of the interesting observations or lessons of the last day has been that least one of these dyes, FD&C Blue Number 1, does appear to breach the blood-brain barrier, I assume in adult animals as well as immature ones.

Would you clarify that?

DR. TAYLOR: I don't know if we actually have

the data in children. I think the animal studies that have been done that show it crosses the blood-brain barrier have been done in adult mice.

DR. CASTELLANOS: It strikes me that that -- I mean, that's a complete novel finding, for me, and it seems like something that consumers might be interested in appreciating.

I don't know if Number 1 is used to make M&Ms blue, but knowing that a particular dye is likely to cross into someone's brain, would you agree that that might be something the FDA would want to let the population know about?

DR. TAYLOR: Well, I think it's an interesting question, and I think one of the follow-on questions to that is how much does it take to actually get to the point where it crosses the blood-brain barrier. These studies that were done in mice, I believe they used gram quantities of Blue Number 1.

DR. CASTELLANOS: How much crossing the brain makes a difference? We don't know that either, right?

DR. TAYLOR: Yes. So these are done at very, very high dose levels, not above the LD-50. The

animals weren't being treated with toxic levels. The LD-50s for these dyes are very, very high.

So we're talking about huge amounts of this stuff going into the system, thousands, or, in some cases, probably tens or even 100,000 times higher than would be a typical exposure in a full day.

DR. CASTELLANOS: But, again, you've mentioned that this is a particularly unique compound, in a sense. So it may well be that there are transport mechanisms or other kinds of active processes that are involved. Certainly, we don't know about that.

DR. TAYLOR: We just don't know at this point.

DR. CASTELLANOS: It's an open question. But it sounds as if, it's on the record, that this is at least one dye in which there is an awareness that it does breach the brain, and there's no doubt about that is what I'm hearing.

DR. TAYLOR: Yes. Interestingly --

DR. CASTELLANOS: How much of its relevance is a different question.

DR. TAYLOR: I think relevance is very important, obviously. This is also, I should say, not

one of the dyes that's commonly studied when these hyperactivity causal relationships have been evaluated.

DR. CASTELLANOS: Granted.

DR. TAYLOR: I think there is some data, but certainly, because it's not an Azo dye, it wasn't included in really the most robust analysis.

DR. CASTELLANOS: A couple more things, and I'm realizing that time is very short. As you mentioned, the European Food Safety Committee, on the basis of the Southampton work and the fact that it was focused on the Azo dyes, now requires labeling -- or the European Parliament, rather, has decided that those Azo dyes that were in the Southampton study carry a label that they may have effects on attention and activity in children. Correct?

DR. TAYLOR: Yes.

DR. CASTELLANOS: Would your organization be opposed to that characterization that does not impute causality, but that describes that there is some evidence that this may in fact be a relationship that individuals should know about?

DR. TAYLOR: I think that, yes, we're not in

favor of that. I don't think the science is clear at this point. I think the studies are intriguing --

DR. CASTELLANOS: You would say that the science is not clear that there may be a relationship.

DR. TAYLOR: I think that there could be a subset with a unique intolerance. I think that the FDA review is pretty thorough and suggests that, but I just don't think that that warrants a specific warning label for the entire population.

DR. CASTELLANOS: So if the Southampton study had had differences between placebo and the drinks that had exceeded the standard threshold of significance of .05 for all four of those comparisons, would that then cause your threshold for asserting that there is evidence that there may be a relationship that consumers should be aware of?

DR. TAYLOR: I think as soon as you start to say "may affect" and "probably" or "possibly," it doesn't necessarily provide consumers --

DR. CASTELLANOS: Well, "may" is different from "probably."

DR. TAYLOR: As soon as you say "may affect,"

I don't think that necessarily provides consumers with the type of information that they would really value. I think that there are a lot of unknowns in the Southampton study, a lot of things that should be followed-up on, but I don't necessarily think at this point that there's a clear causal effect related to color additives.

What we know is that the mixtures apparently cause a statistically significant increase. We don't know whether that's due to one of the color additives that are used here in the U.S., one of the color additives that's not approved for use in the U.S., but that's allowed for use in Europe. We don't know whether that's related to sodium benzoate. We don't even know whether the preservative sodium benzoate may have caused an effect to preserve something within, say, the placebo or the vehicle mix that was lost because there was no preservative present.

So I just think there's really a lot of unknowns here, and I think going to a warning label approach for something that just hasn't really thoroughly been verified is very, very challenging.

And I think, again, if we were talking about the specific mixtures -- so if there was a food producer that used the mixtures within the Southampton study, I think the evidence there is probably pretty clear.

So you add in sodium benzoate, you add in quinoline yellow, you add in Yellow 6 and Red 40, then, yes, I think you could say there is definitely statistical significance for the mix. But for the individual colors, we just don't have that information yet.

DR. CASTELLANOS: Finally, it sounds --

DR. ACUFF: We're going to have to -- okay. One more and then we have to move on.

DR. CASTELLANOS: Let me just make this clarification.

It sounds as if one of the things the industry would like, or maybe I'm overhearing this, is guidance from agencies such as the FDA regarding the kind of development neurotoxicological basic testing that would provide some way forward, because we're not going to get it by using children as, quotes, "guinea pigs," but there are now quite sophisticated ways of examining

developmental rodents and other animals in order to determine whether or not there are behavioral and cognitive differences related to exposures.

It sounds like you would be open and, in fact, welcoming of that kind of guidance.

DR. TAYLOR: I think -- as I said earlier, this issue has been out there for a long time, I mean, since the 1970s. We would love to see sort of a conclusive way, or as close as possible to a conclusive way, to carry out good studies that would be robust, internationally accepted, and that could really perhaps get to the heart of this issue.

We recognize that that certainly takes time. It's certainly not resource -- it's very resource-intensive, I guess I would say. But I think both in terms of protecting consumer health and also protecting long-term viability of the color industry, those are the types of studies that ultimately are going to have to be done. And we need good guidance not necessarily just from the FDA, but from the experts throughout the world that can help us develop those types of guidelines.

DR. ACUFF: Thank you, Dr. Taylor, and we appreciate your time.

All right. We're going to skip the FDA presentation. No, I'm just kidding.

[Laughter.]

DR. ACUFF: I just thought I'd get everybody's blood pressure going.

The next speaker is Jason Aungst, and he will be presenting the FDA evaluation of studies on color additives and ADHD.

Dr. Aungst, whenever you're ready.

Hold. We're going to take five-minute break and then come right back.

(Whereupon, a recess was taken.)

DR. ACUFF: All right. We need to go ahead and get started.

Jason, you can start whenever you want to.

DR. AUNGST: Thank you.

Good morning or afternoon, I'm not sure what time it is. My name is Jason Aungst. I'm a toxicology reviewer in Office of Food Additive Safety in the Center for Food Safety and Applied Nutrition, and I'm

going to present our evaluation of the studies on artificial food colors and behavior disorders in children.

So in this evaluation, we covered over 35 years of research. So I apologize, the following slides are going to be a bit dense, but I will try to get through this quickly. I'd also like to point out the disclaimer that the findings and conclusions in this presentation have not been formally disseminated by the FDA and should not be construed to represent any agency determination or policy.

Just to start off, I'd like to discuss a little bit on attention deficit hyperactivity disorder. Dr. Chronis-Tuscano gave us a great presentation yesterday on the signs, symptoms and effects of ADHD, so I'm just going to touch on a few points here.

ADHD is characterized by inattention, hyperactivity and impulsiveness. As anybody with children knows, these are normal types of behaviors observed in all children at one time or another under different circumstances.

Also, the levels or magnitudes of behavior

vary depending on the child and the situation. It's when these spectrums of behaviors occur in a situationally inappropriate manner, persists over a prolonged period of time at a high level of severity that may be indicative of ADHD. Also, symptoms of ADHD include possible association with learning disabilities and an occurrence in multiple settings, such as home, school or clinic.

The reasons for onset of ADHD are still not quite understood. There are a number of proposed factors that have been brought up that may contribute to its etiology, such as environmental and genetic effects, allergic or immunologic responses, or psychosocial or dietary issues, or a combination of any of these.

Interest in a possible connection between diet and colors, or diets and behaviors, came to the forefront of science in the early to mid 1970s, when Dr. Feingold put forth his hypothesis that food additives such as artificial food colors and flavors and natural salicylates could trigger or exaggerate behavioral disorders or learning disabilities.

Dr. Feingold claimed that children with problem behaviors, when exposed to a defined elimination diet, their behaviors would improve noticeably and that deterioration would reoccur with re-exposure to these components, noted here. Dr. Feingold's observations stimulated this field of research and the continued use of the Feingold diet to this day, as we heard yesterday from the Feingold Association.

Since that time, in the last 35 years since these observations, a number of clinical reports, trials, and commentaries and analyses have been published on this topic. For our evaluation, we focused on those clinical trials with a proposed association between artificial food colors and problem behaviors.

Like I said, our goal was an evaluation of the possible role artificial food colors in triggering or exacerbating problem behaviors related to ADHD in susceptible children. To that end, we reviewed 33 clinical trials that either focused on or included artificial food colors, and most of these trials had

either specific elimination diet or specific color challenges or other relevant food items.

I would also like to point out here that in our evaluation, we considered all of the data from these trials, whether that was positive, negative, or equivocal, and this was all included and considered in the evaluation. Also given consideration was a 1982 NIH consensus statement on defined diets and childhood hyperactivity, as well as available meta-analyses and animal data.

The 1982 NIH consensus statement on defined diets and childhood hyperactivity was by an expert review panel that examined many of these trials, primarily focused on the Feingold diet, and then offered conclusions and recommendations.

For our review of these trials, there were a number of criteria that we looked for to provide a proper assessment of the reliability, the relevance and interpretability of the findings. Those criteria are listed here and were compiled with the consideration of a number of other groups, such as NIH and Dr. Schab's analysis, as we heard yesterday.

While all these criteria were considered important, there's two I've highlighted that, when adhered to, provide an extra level of confidence in the findings or conclusions from a trial. The first is verification of effectiveness of blinding particularly for behavioral raters, and this was important especially for those studies that used only parental ratings as data.

Although in many of these trials, there were panels or groups of researchers to determine the effectiveness of a blinding, many times this wasn't carried over to the home setting; that is, the parents or children weren't surveyed to determine if the treatment was indistinguishable from the placebo. Where this was done, this provided extra confidence that the blind wasn't broken and extra confidence in the findings and the conclusions from that trial.

The second I've highlighted is confirmatory sources of outcome data, and that is just what it says, the use of multiple forms of testing or outcome data to provide additional support for a finding or conclusion.

So for this evaluation, we broke the trials

into two groups based on diet or test article. The group one trials had a specific focus on artificial colors and adverse behavioral effects in children to assess the validity of the Feingold hypothesis.

Of these 26 trials, two were diet crossover trials where the test populations were assigned either to the Feingold diet or to a placebo diet for a defined period of time and then crossed over to the other diet.

Twenty-four of these trials were challenge trials, which included placebo-controlled challenges with select artificial food colors. So of these 26 trials, two diet trials and 14 of the challenge trials were conducted prior to the NIH consensus statement. The remaining 10 trials were conducted following this time.

The group two studies had more of a focus on assessing the adverse effects of food itself in hyperactive and problem behavior children. The test populations were maintained on oligoantigenic or few foods diet, which is more restrictive than the Feingold diet in that it excludes all food additives, including colors, and food components assumed to provoke adverse

reactions in children. The test then was to reintroduce to the suspected provoking food and measure the behavior response.

So we start with the group one studies, and these trials were all designed to be conducted under double-blind, placebo-controlled conditions, using either the diet crossover or specific challenge. And like I said, the diet crossover trials were meant to test the efficacy of the Feingold diet in improving behaviors in problem children.

The specific challenge trials were conducted in children diagnosed with either ADHD, with problem behaviors, or from the general population, included artificial food colors and occasionally food preservatives. These test populations were maintained on a defined elimination diet, and in 18 of these studies, the test populations were specifically chosen because they reported as sensitive to the Feingold diet, and that was for the purposes of trying to maximize the detection of a behavioral effect due to a challenge.

These trials included a number of types of

outcome measures or endpoints that were examined. Many of the studies used subjective assessments, such as behavioral rating scores, usually conducted by the parents, but sometimes also by teachers, clinicians, or other trained personnel. Some of the studies used an objective assessment, such as learning or attention tasks.

A few of the studies combined multiple forms of outcome measures or multiple forms of testing to produce aggregate behavioral scores, and this goes back to our criteria of confirmatory sources of outcome data. In fact, two-thirds of these studies did use multiple outcome measures to try to support conclusions and findings.

So based on those studies conducted prior to 1982, we found equivocal findings of improved behavior in Feingold's diet or adverse reaction to color challenge, and this was only in a small subset of children with problem behaviors and presumed sensitivity to artificial food colors. Those numbers are noted here.

Two were concluded as positive, six as

negative, N/A as equivocal. And I should point out that the level of confidence varied across these individual trials.

The studies conducted following the NIH consensus statement, we found some responses to color additive challenge, typically in subsets of children, and that these responses were not typically representative of a hyperactivity syndrome, but rather were reported more as irritability, fidgetiness, and sleep problems. And these similar behaviors were reported across multiple populations, such as in problem behavior children or children with ADHD.

Another important note here, if you remember from a previous slide, I had mentioned that 18 of these studies, the test populations were specifically chosen because they were sensitive to the Feingold diet. Of those 18, only two were concluded as positive for having effect with artificial food colors. So this suggests that if parents really are seeing effect of the Feingold diet, it's more likely due to some other component in the diet rather than artificial food color, and that could be a flavor, a different

additive, or just some general type of food that was removed from the diet.

There were a number of caveats and limitations that were noted during the review of these trials. This is a collection of those. For example, equivocal findings, such as positive parental ratings and negative ratings from clinicians and teachers. Other examples were treatment order effects, blinding issues, or missing data. But I want to point out that not all these caveats and limitations applied to every trial. This was just the collection from the group.

So based on the studies conducted prior to 1982, the NIH consensus panel concluded that there was a limited positive association between the defined diets and a decrease in hyperactivity that involved only a small proportion of patients and that these decreases in hyperactivity were not observed consistently.

They also concluded that small group of hyperactive children on defined diet experienced an increase in hyperactivity when given moderate doses of artificial food colors and that, again, these increases

were not consistently reported by teachers, parents and observers. There was a meta-analysis completed shortly after this time, which included many of these similar studies, which also came to similar conclusions.

Based on our evaluation of the studies conducted prior to 1982, we also found similar conclusions to this NIH consensus statement in the meta-analysis, and that was that the findings were suggestive of limited beneficial effects of the Feingold diet in hyperactive children and that the findings also showed a limited association between artificial food colors and behavioral changes in this small subgroup of children with hyperactivity or problem behaviors.

As we heard yesterday, a meta-analysis conducted by Dr. Schab, which included some of those trials that were completed after the NIH consensus statement, provided the conclusions that the findings were suggestive of a limited association between artificial food colors and hyperactivity behaviors and also that these findings were suggestive of provoking general behavioral disturbances rather than hyperactive

symptomology.

Again, the sensitivity to artificial food colors may not be limited only to hyperactive children. Based on our evaluation of the studies conducted following NIH consensus statement, we found that the findings were suggestive of possible intolerance to artificial food colors in certain susceptible subgroups of problem behavior children with and without ADHD and possibly certain susceptible children from the general population without particular behavior problems, and that these were typically small to moderate behavioral changes which may not necessarily be characteristic of the ADHD syndrome.

So based on our evaluation of those 26 trials, our overall conclusion was that certain subgroups of children with problem behaviors that may or may not be related to ADHD and possibly certain children from the general population without particular behavioral problems may exhibit a unique intolerance to artificial food colors, resulting in typically small to moderate behavioral changes, which may not necessarily be characteristic of ADHD syndrome.

So while the group one trials focused more on artificial food colors, the group two trials had more focus on assessing the effects of food itself in hyperactive and problem behaviors in children. These were the trials that used the oligoantigenic or few foods diet. And, again, these trials were designed to be conducted under double-blind, placebo-controlled conditions. In the two diet crossover trials, the test populations were maintained on an elimination diet or placebo diet and then crossed over to the other diet.

The specific challenge trials were conducted in children diagnosed with either ADHD or problem behaviors and consisted of three phases. The first phase was a non-blinded identification of the test population. Phase 2 was a reintroduction of a suspected provoking food item to develop a non-blinded baseline. And then phase 3 was the double-blind, placebo-controlled challenge using one or more of the suspected provoking food items to verify and assess any behavioral effects.

Again, these trials used a number of types of outcome measures or endpoints. Many of those used

subjective assessments and some objective assessments. And a few of the studies also included skin prick tests or measurement of serum IgE levels to test for atopy or a possible immunological response.

So based on review of those studies, we found some responses of intolerance to suspected provoking food items in ADHD or problem behavior children. Those numbers are marked on the right. And, of course, the level of confidence varied across individual trials. We also find some evidence of a small increase in hyperactive behaviors, and, as we saw with the group one trials, other behaviors, such as irritability, fidgetiness and sleep problems.

Of those studies that examined a possible allergic response, we found equivocal findings regarding atopy, although there was a desensitization study suggesting that the behavioral responses were not mediated by an IgE mechanism. Again, there were a number of caveats and limitations that were noted during the review of these trials, and, again, not all of these applied to every trial.

So based on the evaluation of these seven

trials, we concluded that the children with ADHD or other problem behaviors may exhibit a unique intolerance to a variety of foods and food components, including, but not limited to, artificial food colors, and that these behaviors were associated more with irritability, fidgetiness and sleep problems rather than attention deficit and learning deficiency or a hyperactivity syndrome. The studies also suggest that this food intolerance may involve some type of immunologic process, possibly involving a non-IgE cellular response to an antigen rather than an antibody-mediated immunization.

So in evaluation of these trials, we considered dietary conditions, whether it was the Feingold diet or another elimination diet, the test article or challenge article, such as artificial food colors or various provoking food items, the test populations, ADHD, heterogeneous behavior problems, the general population, diet responsiveness, as well as the methodologies and limitations of the individual trials.

Just to reiterate our conclusions, based on the evaluation in the group one trials, which had more

of a focus on artificial food colors, we concluded that certain subgroups of children with problem behaviors that may or may not be related to ADHD and possibly certain children from the general population without particular behavior problems may exhibit a unique intolerance to artificial food colors, resulting in typically small to moderate behavioral changes which may not necessarily be characteristic of ADHD syndromes.

In the group two trials, which had more of a focus on foods and food intolerance, we concluded that certain children with ADHD and/or other behavior problems, when exposed to various provoking food items, including artificial food colors, may result in behavioral changes associated more with irritability, fidgetiness and sleep problems rather than attention deficit and learning deficiencies or hyperactivity syndrome.

While these trials examined possible effects, very few tried to address possible underlying mechanisms. These following bullets are a collection of suggestions and possibilities raised by

investigators across multiple studies, such as are these effects possibly due to some toxic, neurotoxic, physiologic, allergic, or immunologic process; are the potential behavioral effects caused by one particular color or food item or by the combined action of multiple food items or by some interaction, perhaps synergistic, with other components in the food; are these potential effects associated with some factors that predispose children to ADHD or other types of behavioral pathology or could the effects be associated with some predisposing factor not necessarily related to behavior disorders?

While investigators have speculated about possible mechanisms, these basic questions remain largely unanswered.

The next few slides are going to examine some of the available information concerning possible biological mechanisms. Of course, neurotoxicity of artificial food colors is one hypothesis that's been put forward, and along those lines, a variety of animal studies have been conducted to determine whether there's biological support for a color ADHD effect or

hyperactivity effect.

Probably one of the most well studied colors is erythrosine or Red Number 3, as we heard earlier. Initial studies on this chemical suggested a possible dopaminergic action, but were later shown to be a nonspecific interaction rather than a specific neuronal effect.

Studies in the following years also showed either no neurotoxicity effect, a non-dose-response-related effect, or minimal effects at high doses. Similar effects of non-variable or minimal effects have been reported for a number of other chemicals tested, including some natural dyes, and some of those are listed at the bottom point.

These are just some of the studies we examined up to the point of this review, and more studies continue to become available and we will continue to monitor those as they do. But currently, the available information has not established any clear link specifically between color additives and hyperactivity.

Although the neurotoxicity studies were inconclusive, hypotheses concerning dopaminergic

involvement continue to arise, and this is based on the view that alter dopaminergic neurotransmission may be involved in the pathophysiology of ADHD. And since there are therapeutic treatments that are known to target the dopaminergic system and affect ADHD, it logically follows that any other treatment, for example, colors that would possibly affect the dopaminergic system, could also affect ADHD.

Histamine is another neurotransmitter that's been hypothesized to play a possible role in color effects. There are many environmental factors that can cause an increase in the release of histamine, such as infections, food items, and even certain artificial food colors. And since there are genetic polymorphisms involving histamine genes that can impair histamine clearance and there are histamine receptors present in the brain, this provides a possible mechanistic basis for gene-food interactions, as has been suggested with ADHD. Also, we heard some additional information yesterday from a recent study from Dr. Stevenson that the genetic variants related to histamine could possibly play a role in modulation of behaviors.

There is a strong genetic component for ADHD, which raises a possibility that genetic processes may underlie a link between colors and hyperactivity or ADHD.

There appears to be a number of interacting biological and environmental factors that are involved in the expression of ADHD, and food may be one of these risk factors to list or exaggerate, but not cause hyperactivity behaviors in some children. It remains to be determined if the gene variants associated with ADHD are also the variants associated with modulating food sensitivities.

Some suggestion for this does come from a study by Rowe & Rowe, where more hyperactive children were reported to react to a color challenge than normal children, suggesting a possible genetic predisposition for hyperactivity and sensitivity to food colors. However, the behaviors reported by Rowe & Rowe differed from the behaviors associated with ADHD. And this was also the case for the food intolerance trials, which reported behaviors not characteristic of ADHD.

So these color effects have not been

consistently associated with atopy and generally believed not to be due to an IgE-mediated mechanism. That leaves open a possibility of some other pharmacological action, such as non-IgE-dependent histamine release.

In support of a food intolerance issue, many of the children with reported improvement on the Feingold diet did not respond to color additives, and this suggests that other factors in the diet could be responsible.

Following the NIH consensus statement recommendations, many studies began expanding into any food item suspected of causing an adverse reaction with the idea of individualized sensitivities or that multiple foods may provoke adverse behavioral reactions.

Additional support for an immunologic reaction comes from a study where children with ADHD were successfully desensitized to food items that previously provoked adverse behavioral actions, and these data and hypotheses are more suggestive of certain children having a predisposition leading to a food or color

sensitivity rather than a direct neurotoxicity.

This is more in line with our overall conclusions that exposure to food and food components, including artificial food colors and preservatives, may be associated with behavioral changes, not necessarily related to hyperactivity, in certain susceptible children in ADHD and other problem behaviors and possibly in susceptible children from the general population.

The findings also suggest that this food-related triggering of behavioral changes is not due to an inherent neurotoxic property of the food or food components, including artificial food colors and preservatives, but appears to result from a unique intolerance exhibited by certain predisposed children to a variety of food items and color additives. The etiology of this type of unique intolerance is unclear but may involve generic endocrine or immunologic pathways.

So just one final slide to summarize some of the findings and implications is that this data is suggestive of predisposition for food intolerance or

food hypersensitivity in certain children and that the triggering food or food component may be different for each child.

These behavioral responses to food, food component, additive, flavor, or artificial colors appears to depend on the individual and not on the class of provoking item. This suggests that these food components in the diet, whether it be milk, orange juice, flavors or additives or artificial colors, are not inherently neurotoxic, but that the response to the provoking item will depend upon the individual person.

With these individualized sensitivities and a lack of understanding of the mechanism behind this food intolerance, the current FDA regulatory labeling requirements provide information for identifying individual ingredients and enabling personal avoidance to avoid these ingredients, if that's what's desired.

Thank you very much. I'd welcome any questions.

DR. ACUFF: Thank you, Dr. Aungst.

Do we have any questions? Dr. Castellanos?

DR. CASTELLANOS: Thank you. That's an

excellent review. I'd like to clarify or correct one misstatement. You've mentioned fidgetiness, irritability and sleep several times as some of the behaviors or symptoms that were associated with some of these manipulations, and fidgetiness is one of the core 18 criteria for ADHD that's included in the DSM-IV. In fact, it's the single symptom with the highest positive predictive value in children. So it's very much a part of ADHD, as we conceptualize it. Among the DSM-V panel that's revising the diagnostic system or attempting to, we struggle with these sorts of issues, but we're not doing away with fidgetiness as part of hyperactivity.

Secondly, irritability, unfortunately, is a very broad symptom that's present in many disorders, but it's also a key, core symptom of oppositional defiant disorder, which is very frequently associated with ADHD, in about 40-50 percent of cases. So it may well be, again, part of a larger complex that we're not exactly clear of how to understand.

Finally, sleep problems are clearly greater in terms of their prevalence in individuals with ADHD, and there's a lot of questioning about chicken-and-egg

issues, because sleep problems produce difficulties with regulating one's behavior, with attention, concentration, and may well be sort of tied up in a kind of mechanistic complex loop.

So it sounds as if part of what you've concluded is that there is some evidence of association with behavioral changes that may not be, from your perspective, classic ADHD, but certainly would fit in a larger constellation of symptoms that are associated with problems associated with ADHD.

DR. AUNGST: Of course. And those behaviors, too, are also associated with a number of other syndromes or characteristics, such as a food intolerance. Of course, irritability is going to come from that, sleep problems can come from that, and fidgetiness, as well.

As we're characterizing it here, it's according to the DSM manual, where it's required to have six of those components over a certain amount of time, and these are being expressed more transiently and can clearly be linked to other issues. I know the fidgetiness and some of these other components are

related to anxiety or mood disorders as well. I believe that was one of the parts of the DSM, is that as long as it's not one of these issues, then we go with ADHD.

DR. CASTELLANOS: Well, that's not exactly right. But at any rate, I guess the point here is that I don't understand our charge as focusing exclusively on the construct of ADHD. If it were to be the case, I would suggest that we not do that. ADHD is constructed by a committee very much like this one that was struggling to do the best they could to describe an elephant without being able to see it, and we don't have a pathophysiology of ADHD at this point. We're kind of groping towards one.

So that's not the issue. Behavioral effects, symptoms, whether they be fidgetiness, irritability, sleep difficulties, are very much -- those are real issues, whether or not they're part of a larger ADHD diagnosis.

Would you agree with that?

DR. AUNGST: Yes, those are. Those are, and I think it's very important to get to the underlying

cause of those, whether --

DR. CASTELLANOS: Well, again, "causes" is a very tricky word here.

DR. AUNGST: Yes.

DR. CASTELLANOS: We typically don't think in terms of single causes any longer. Everything is multi-determined. There are genetic factors that predispose. Parents carry those genes, but they also carry their own parenting history. Epigenetic factors come into play.

There are multiple loops of bidirectional causality that make it essentially impossible to sort out cause. It's a question of contribution and whether or not distributions of behaviors and proclivities are shifted one way or the other.

DR. AUNGST: Yes.

DR. ACUFF: Dr. Voorhees?

DR. VOORHEES: Thank you. I believe I heard you say that part of your interim interpretation was that it did not appear that the food colors were associated with neurotoxicity. I'm not quite clear.

Do you really feel that you have adequate

data, studies that have been specifically directed at looking for potential neurobehavioral toxicity to be able to make the interpretation that these are not in fact associated with neurotoxicity? I'm not clear how you reached that conclusion.

DR. AUNGST: Well, these behaviors, like we say, could be indicative of other symptoms, such as food intolerance, and neurological effects could be secondary to that.

Of course, it would be with things like irritability, anything that would affect behavior. But the data weren't suggesting that due to the variability in the response, the variability between subjects, the magnitudes of the response, there's no indication that it's directly targeting a certain neurologic target to produce a standard neurotoxic effect.

DR. VOORHEES: You also cited the animal data, but you don't have animal data that speaks directly to the issue of whether or not there's developmental neurotoxicity. I think you actually cited a study I did, and I don't normally criticize my own studies, but I will criticize that one.

[Laughter.]

DR. VOORHEES: That's 30-year-old data, using 30-year-old techniques that do not represent how neuroscience has advanced over the last 30 years. We can do much better than those kinds of studies.

So if you're relying on 30-year-old data, I would suggest that that's not an adequate basis to make a determination that the preclinical studies have ruled out the possibility that these might have developmental neurotoxicity.

DR. AUNGST: Well, to address that, from many of the colors that have been approved, I know you raised a question at the last talk about the two-year studies, and I found out that five of those six most commonly used colors were based -- the ADIs were set on those two-year studies, which included in utero exposure and include also very high dose levels, up to the maximum tolerated dose. And by doing that, we capture the developmental period from the point of conception through life at very high dose levels. And during examination of those trials, a number of neurotoxicity screening issues are observed or examined

to determine if there is a need to go further with specific neurotoxicity testing.

DR. VOORHEES: Did any of those studies include neurobehavioral outcomes?

DR. AUNGST: Not specific neurobehavioral testing, but clinical observations of lacrimation, clinical observations of behaviors in the normal cage setting.

DR. VOORHEES: Which are known to be completely insensitive.

DR. AUNGST: It also includes histopathology afterwards of all neurological systems.

DR. ACUFF: Dr. Freeland-Graves?

DR. FREELAND-GRAVES: You just said that it included five of the six colors tested. One did not include in utero study. What color was that?

DR. AUNGST: I would have to confer with colleagues and get back to you on that. I don't know exactly which one it was. I said the ADIs that we have, those ADIs were based on -- five of those were based on those two-year studies. I'm not sure what the other ADI was based upon. It could have been

additional studies.

DR. ACUFF: Dr. Fenner-Crisp?

DR. FENNER-CRISP: I'd like to extend Dr. Voorhees' questions and make a comment that I would submit that the value of the chronic bioassays that were the basis of the ADIs would have no value in assessing any kind of neurological responses.

As you point out, the kinds of cage-side observations that are done as a quick screen in those studies don't tell you anything.

DR. ACUFF: Ms. Lefferts?

MS. LEFFERTS: We heard earlier about some really important issues about dosage, that many of these studies were performed using pretty low doses compared to what kids these days are being exposed to. Yet, I didn't see that in your list of criteria nor sample size. Again, if we have a weak study and we're using low doses, we're obviously going to miss -- we're in danger of missing effects, but yet, miraculously, some of the studies actually do see effects on behavior.

Considering the presentations you heard

regarding those issues and also, of course, duration between exposure and the measure of outcome, would you, on reflection, believe that those would be important criteria to include?

I guess the second part of that question is about whenever -- every study has a weakness, has many weaknesses, but we want to look at are those weaknesses likely to take us toward the no or take us toward finding an effect when there really isn't one.

Did you do that kind of analysis? It seems to me that some of the weaknesses in the study would be biasing toward against finding an outcome, yet we often do, particularly the dosage issue.

So if you could comment on those.

DR. AUNGST: Okay. For the dosage issue, there have been a number of comments about that.

Part of a dose-response -- a dose-response is wonderful. It's something we love to see. It's something very difficult to do in a human population, especially using very large populations, but even in small populations, where we did see some effects.

With a dose-response, we'd like to see a

change in the magnitude of effect with the dose-response more than just how many responded. And I think page 96 in our interim report has an entire section on the dose and suggests that whether it was a high dose or a low dose, the effects were not associated with the dose. It's the effects at high doses could be at the same magnitude as those seen at the low doses -- this goes back to suggesting more of a general issue -- and that the effects did not increase with increasing dose across studies.

Your other question was based on the timing of treatment, and of course we think the timing of treatment is very important for understanding the findings and the conclusions made.

For example, I know the Feingold -- not the Feingold -- Dr. Stevenson's study has been brought up, and the issue was are the parents only seeing the effects, because the effects are only happening during the treatment time at home, and it's wearing off before the kids to get to school or they're only getting their treatment after school. In some of those studies, I believe it was noted that I think the 8-year-olds

either had their juice before or after school. So in those cases, we would have expected to see some teacher effects there, where we didn't.

So I think you're right. It's very important to have as much data as possible, including when the treatment was given and when the outcomes were measured, and that way we can get a better assessment of what the effect truly is and the duration of effect.

MS. LEFFERTS: I'm not aware that any of these studies used very high doses. They all seemed to be pretty low doses. I mean, of course, some are higher than others, but I think it would be a mistake to characterize any of these studies as using high doses.

DR. AUNGST: Well, I said that's comparatively across the range of studies, then, the studies that used the higher doses.

MS. LEFFERTS: But I think it is very important to consider what children are eating or might be expected to eat, reasonably expected to eat, and those levels have not typically been tested.

DR. AUNGST: That's an important recommendation for future studies then.

DR. ACUFF: Dr. Jones?

DR. JONES: Tim Jones. Ms. Lefferts, your questions are good ones, but I would say that if one of the criteria that had been on the list was adequate sample size to show statistical effects, there would be almost no studies left on the list to be talking about.

DR. AUNGST: Yes.

DR. ACUFF: Dr. Castellanos?

DR. CASTELLANOS: One of the puzzles that's confronting the committee is the lack of clear agreement between multiple observers, in particular, parents and teachers, and it's I think an embarrassment that the field has to deal with, that that is the case for 40 years. Forty years' worth of data show us that parents and teachers agree in the best of cases with the correlation coefficient of about .35; in other words, about 10 percent of the variants are shared.

We don't understand why that is. The context is a huge part of this. It's also the fact that we use essentially checklists, as you heard, not at all, just a little, pretty much, very much is basically the standard in the field, and that's sensitive. Those

were designed to detect medication effects, but because there is an absence of other real measures, that's become the standard. But the result of that is that, again, the context is a huge part of this and it's something we have to deal with, and we don't know which one is the right one to look at it in any given situation.

We heard yesterday that the ratio of the effect sizes between parents and teachers can flip from 2 to 3 to 1, or 5 to 1 to 2 to 1 in the other direction, et cetera. So it's a real issue that does tend to wash out results. There are two kinds of errors that you were asked about, and the blind is one that's likely to produce a type I error, if a blind is penetrated.

Having said that, the question of do you know which phase this is, is very problematic. For example, in stimulants, you can have a blind that looks -- a placebo that looks exactly like the molecule, the active treatment, but parents are very rarely food because of the clear medication effects. So they know which is the placebo phase and which is not, not

because the formulation wasn't adequately put together, but because they're looking at the behavioral readouts. So that is a standard that you put there that may not always be the best one.

But at any rate, the other one of the insensitive measures is, again, one that tends to minimize results. And so when something does emerge, it's probably, against that background, a great deal of noise.

DR. AUNGST: Yes, that's true. You've raised many good points. And for the first point, with the verification of effectiveness of blinding, where we're surveying the parents or child, that criteria was included. If that was adhered to, like I said, it provided a higher level of confidence in those findings. It's not that we discounted a study if it wasn't done, because we had many studies where it wasn't. It was just that would add more confidence in our minds that this truly was an effect and not a possible break in the placebo or the blind.

I forgot your second point.

DR. CASTELLANOS: Just the issue that the

unreliability of our measures tends to really increase the effect sizes in the field.

DR. AUNGST: Sure. Sure, yes. Yes. And that gets back to the general questions that always are raised Are the parents looking at the same behaviors as the teacher or the clinician? Are the parents more in tune with certain nuances of their child's behavior where the teacher isn't, or is the teacher looking at specific learning deficits? Yes. That makes things a little more difficult.

DR. ACUFF: Dr. Vugia?

DR. VUGIA: Thank you. Duc Vugia. I want to get back to the dose-response. There was a paper by Rowe & Rowe in 1994 that was double-blind, placebo-controlled, where children were given once a day, in increasing doses, 1, 2, 5, 10 and then 20 and 50 milligrams; so not really great doses at the end, but still there was an increasing dosage. And the parents' rating did report increasing behavioral effects, suggesting that there is a dose-response effect, according to this study.

I just want your comment on that again, as to

why you think that -- you mentioned that your thinking is that there are many papers on dose-response, which I agree with, but on the other hand, what was your consideration of that paper?

DR. AUNGST: Well, like I say, there were a number of issues with that paper, although the dose-response is something that adds much more confidence in the findings is what really stuck out for us. And it was interesting to see that dose-response in the hyperactive children. An additional note was that that was also noted in some of the non-hyperactive children, suggesting this really isn't focused just on that population.

But what that also shows is it's important also to look at the individual color and where there was an effect there, we saw a dose-response. And although those colors were low, the effects rated there did max out I believe at the 10 milligram level, and there was a plateau level there, which could suggest why we would see these studies that used even higher doses had the same effect as maybe one of these lower doses. That was part of that.

DR. ACUFF: Dr. Fernandez?

DR. FERNANDEZ: I have a question regarding the food colors that were used for the Southampton study. I know that two of those colors were not approved in the United States. Do you know why?

DR. AUNGST: I would have to check into that, and I can get that information for you later this afternoon. I don't know why they weren't used here.

DR. FERNANDEZ: Okay. Thank you.

DR. ACUFF: Okay. Thank you very much, Dr. Aungst.

DR. AUNGST: Thank you.

DR. ACUFF: We are moving into the public comment session, but we have some housekeeping to do, and I'd like to recognize Carolyn Jeletic.

MS. JELETIC: So while those housekeeping chores are going on, I just need to make a quick statement.

To the public speakers, I'd just like to remind you, at the beginning of your public speaking statement, that you please provide a statement that would advise the committee of any financial

relationship that you may have with any company or group that may be affected by the topic of this meeting.

You each have, as you know, five minutes for your remarks. When you begin to speak, the green light will appear, the lights right here. The yellow light will appear when you have one minute remaining, and at the end of the five minutes, a red light will appear, and your presentation should be completed by then.

Since we have a number of speakers and we're running behind schedule, we're asking you to please adhere to the five minutes. We really need you to adhere to the five minutes. Please do that. We do not want to turn off the mic on you; however, we will.

[Laughter.]

MS. JELETIC: So I would also like to tell you that the chairman is the one that will authorize you. He is the only one with the authority to authorize anyone to speak, and this includes the public speakers. So he'll announce your name and you'll come forward. And the committee will be given an opportunity to ask questions of the public presenters at the conclusion of

the open public hearing.

I would also like to point out that under CFR Part 14, this open public hearing, there is a limit time devoted to the public speakers under this type of meeting. So we do have a legal mechanism available to you if you want to make further comments. FDA will accept any written comments, if you submit it to the dockets under Docket Number FDA-2008-PO349, or you can contact me, and I will tell you where to send it.

Thank you.

DR. ACUFF: And just to remind the committee, we will have questions following all the speakers.

Renee Shutters first.

MS. SHUTTERS: Good morning. I first found out the powerful effect of these dyes about two years ago when my little boy started pre-K. Mrs. Bell and I started this notebook because we were having two to three meltdowns per week, and they were pretty bad. I even had the teacher mention to me during the parent-teacher conference that she had a boy the prior year that had problems with dyes, and my reaction to her was, "Well, I don't think that could be it. It's not

like I give him Skittles every day."

So by Christmas, things were just getting worse and worse, and I can tell you I was praying for the answer. And I ended up running into a friend of mine, and the first thing out of her mouth was, "Guess what? We found out that David is allergic to Red 40." I said, "Allergic to Red 40. What does that mean?"

She said, "Well, he ended up getting kicked out of preschool." I'm like, "I didn't know you get kicked out of preschool." And she explained that he was very violent from the Red 40. And she said something to me that helped it click. She said, "It's even in white frosting." Okay. So now my Skittle theory is out.

So I went home and I found Feingold on the Internet, and what I did was I decided to go through my pantry and I removed everything with dyes. I didn't do the preservatives until six months later, because it just seemed too overwhelming for me.

So I went and met with the teacher the following Monday after New Year's, explained, "Hey, we're going to try this dye-free thing." And she says,

"Okay, I'm in." And two dye-free days later, she's braced herself for the meltdown because he didn't get the tricycle. He looks at her and says, "Oh, well. Maybe next time will be my turn." And we had a pretty good laugh about that when she called me that night and couldn't believe the difference. And so I knew at least I was on the right track.

So we were saying our prayers two weeks later and he looks at me and says, "Momma, I think I'm finally happy now."

So we were still having some trouble with hockey, and I'm going to read the letter that his coach wrote for him when I went on my first trip to Washington on this subject.

"To Whom It May Concern: My name is Tom McFall, and I am Trenton Shutters' ice hockey coach. I first met Trenton when he joined the Tim Horton's Timbits beginner hockey program. We skated twice weekly from 2008 to February 2009.

On many occasions throughout the Timbit season, Trent's behavior was not ideal for the program. He often seemed angry and acted impulsively. He was

known to push other children, hit players with his stick, or take his hockey gloves off and place his bare hands on the ice while others were skating, which is very dangerous. Trent would not participate in many of the on-ice drills or activities.

Because of these behaviors, I informed my assistant coaches to keep a close eye on him. During the season, we worked with Trenton's parents to use a behavior incentive plan, where he worked toward earning a sticker for good behavior. While this helped, Trenton remained uncooperative and disrupted.

As the season progressed, it became necessary to assign a junior coach to be Trenton's one-on-one partner at all times while he was on the ice. This helped to minimize Trenton's distractions to others and keep everyone safe on the ice for the remainder of the season.

This summer, Trenton attended a summer hockey camp I directed in July. I had the same junior coach lined up to shadow Trenton throughout the week. However, the child who participated in the summer camp was completely changed from the one who attended the

winter program. This summer, Trenton was always smiling, eager to participate, followed directions, and was a joy to have on the ice. He expressed enthusiasm for each new activity, and his behavior was exemplary.

Trenton's mother indicated that changes had been made to Trenton's diet, producing this dramatic change. We look forward to having Trenton return to hockey in the fall."

He did return to hockey, and he has been written as being a model student, and he actually got student of the month, it just so happens, this month, which, I can tell you, two years ago, I never would have thought was possible, and I was pretty scared.

So I came here on my own expense, and I'm just thankful that you found this out. So I'm here not because of Trenton, because, see, he's going to be okay. I'm here for the others.

Thank you.

DR. ACUFF: Thank you, Ms. Shutters.

Amy Yuter?

MS. YUTER: Good morning. This is the story of a little boy, a boy who came home after his teacher

called and said she couldn't teach him anymore. He stared out the window as she left his side, sucked his fingers, and jabbered uncontrollably with his mouth; a boy with impulse issues; a boy that wanted to listen, to focus, but couldn't.

This is the story of doctors who diagnosed the boy with moderate to severe ADD and put him on speed to help the boy gain control. The medicine was a band-aid, an okay one at best. This is the story of a boy who one day age jelly beans and his symptoms worsened before our eyes, and it wasn't the sugar.

This is the story of a mom that found Feingold diet that night in her Internet search and put the boy on a diet free of food color, free of jelly beans, and not free of sugar. I wondered, "Why isn't this information provided by our doctors? Why isn't it on the nightly news? Why isn't my government telling me the effect food colors can have?"

By Monday, the boy was off his medication and on his new diet for two days. His teacher said it was remarkable. The boy is now excelling in school and is in the gifted program. His teachers are amazed that he

once had focus issues. When he accidentally has some food color, they see the effect it has.

When this boy stopped eating food coloring, he stopped fidgeting, he stopped staring out the window, he stopped sucking his fingers, he stopped acting impulsively, he stopped jabbering with his mouth, he started paying attention well, he started following instructions, he started doing what he was supposed to do. He was happy. He had control of his body.

After removing food coloring, the mom worked with a doctor and nutritionist and tested wheat gluten, sugar, and dairy. All of these foods were added back in with no symptoms, and only the food dyes remain out of his diet.

Why couldn't he eat all that yummy stuff all the other kids ate? He would follow his diet. He was able to say no to food color, as he knew it was bad for him and bad for other kids, too, and that's why this boy is here today.

This is the story of the boy's sister whose stomach aches, hives, headaches and tantrums went away when the yellow cheese curls she ate were taken out of

her diet; this mild mannered child, whose out-of-character outbursts caused her mother to question, "Could it be something she ate?" The boy's sister was hesitant to stop eating food colors, the diet that her brother followed, but if it could make her symptoms go away, she would try it. And they did.

This is the story of a mom whose life improved once food colors left her world, improved focus, ability to sit through meetings. Her performance reviews showed the dramatic difference.

This is the story of the country of the United Kingdom that made changes and the story of Wrigley Company, who now makes color-free Starburst for lucky kids abroad.

This is the story of many, many children and families who need our help. This is America's story, some kids whose moms found Feingold and their kids' symptoms went away in 48 hours; many, many more moms who haven't and just don't know that the pink yogurt they gave their child is causing her trouble; and, many on medication who potentially could be helped.

Let's make a change, the little change in this

boy's life that made such a big difference. You can make a big difference, too.

This is Ben Yuter. This is his sister, Sarah, and I am the mom. Some say my kids are fortunate to have a worrier mom who wouldn't stop searching until she found an answer. My former position as a federal investigator was helpful to our cause. Now, as a compliance officer that continually reviews the risk present in my organization, I frequently do a risk-benefit analysis. This is an easy one. These bright-colored foods offer American children no benefits, but the risk, no. The real effects of these food colors are hurting them each and every day.

Please help make a change. Let them be among many others who are succeeding in life instead of being among the minority. Don't get me wrong. There are plenty of Bens in our neighborhood, in his school and his classroom. We even have a therapist in our neighborhood who will diagnose the Bens with ADD and suggest they start medication, ironic as it is, medication with pretty blue capsules.

I recently went to London on business and

brought back these Starburst that my kids can eat with no problem. These colors are fun and good. They're naturally colored. My kids wondered, "Why can't other American kids have safe candy, too?"

If you are not going to ban these harmful additives, please follow the U.K.'s path in requiring appropriate label warnings so that American parents can make an informed decision as to how to feed their kids.

Thank you.

DR. ACUFF: Thank you, Ms. Yuter.

Next is Ed Takken.

DR. TAKKEN: I'm most comfortable speaking to slides. I'm a retired physicist. And of the awards I've gotten, the one I like most is for innovative research, one of 75 given on the 75th anniversary of the Naval Research Laboratory.

I loved physiology when I was in undergraduate school, but did not take organic chemistry. Since retiring, I've gotten into two things involving biological matters. One that's particularly surprising is that society's concept of how early life evolves is incorrect. I just mention that in passing. And this

talk is taken from this website, and I would like to point out that there is a library in there of testimonials like you've just heard.

These are from the Feingold Association monthly over the last 35 years, and I suggest those are worth reading. There are surprises in there. A thread throughout is surprise that cannot be placebo.

I have no associations in any financial way with other organizations.

This is my main viewgraph. And my point to the committee is that this is what you've been asked to do. Is there evidence evolving now that colors can cause behavior changes in hyperactivity? But I claim that the task to you is hugely bigger. You cannot decide on that issue without also looking at this body of research, which I call the paradigm period of research, it's eight years, and looking at what mainstream medicine has been doing.

You cannot decide this without deciding -- if you decide this in a positive, you're also deciding that these two are wrong. This is monumental. You have a big task.

A key phrase to shape thinking I think is not just to talk about additives or foods, but causality. Is it true or isn't it? Does something cause ADHD or not? Is it innate or is it causal?

The mainstream medicine has been pursuing the path of innate on the basis of that paradigm period of eight years of research right after Feingold. And in my reading of what's happening, this endeavor is not getting very far. In particular, there is no clear model about the phenomenology. And I would describe the modeling there as sort of hopeful bootstrap. I give one example here. There are others.

Let's see. The top is off of this. This is a causal model involving enzymes. It's based on the idea that something causes ADHD. The idea basically is that the body's enzymes for cleaning up waste products may be deficient, and if it is, when you eat more things that put load on a cleanup mechanism, things begin to happen. There's overload in the brain. Apparently, what kicks in to help get rid of this extra load of waste products is extra production of MAO, and that has far-reaching consequences.

This is an interesting point. It fits with what is known here, and this is even interesting. All the comorbid symptoms are not separate things, but in this way of thinking, related. This is what I call a model that has some obvious inconsistencies. It's the kind of thing that's lacking in what mainstream is doing.

Here is a possibility that's not being pursued. Again, this cannot be seen if you think innate. It offers a possibility I think of a test protocol that would solve the placebo and units of measure problems of studies. It's been languishing for 13 years. So far as I know, it's not going to be investigated.

Back to my main viewgraph. So involved with what you've been charged with are these two bigger issues, I'll raise -- I want to call this a false negative. The results of this body of research were that there is no connection between controlled diets and hyperactivity or ADHD.

Okay. I've got to quit. As a compromise of trying to decide on these things, the committee could

at least put on its Web page some of the things that are not being considered, like work something out with the Feingold Association on what they say and tell the public about it.

DR. ACUFF: Thank you, Mr. Takken.

Will Fisher is next.

MR. FISHER: Good morning. My name is Will Fisher, and I'm vice president of science and policy initiatives for the Institute of Food Technologists, otherwise known as IFT.

IFT appreciates the opportunity to provide comments to the FDA Food Advisory Committee on whether available relevant data demonstrate a link between children's consumption of synthetic color additives in food and adverse behavior.

IFT exists to advance the science of food. Our long-range vision is to ensure a safe and abundant food supply contributing to people everywhere. Founded in 1939, IFT is a nonprofit scientific society with individual members working in food science, food technology, and related professions in industry, academia, and government.

IFT champions the use of sound science through knowledge-sharing, education and advocacy, encouraging the exchange of information, providing educational opportunities, and furthering the advancement of the profession.

IFT's viewpoint is that the consumption of synthetic food color additives presents no harm to the general population. This viewpoint is based on our knowledge of available relevant data and research conducted to date. Although the scientific evidence does not show a conclusive link between synthetic food color additives and adverse behavior in children, IFT does support further research in this area to address consumer concerns.

As you are aware, the theory that synthetic food colors are linked to adverse behavior in children gained publicity in the 1970s, largely based on a 1973 presentation and 1975 book by Dr. Benjamin Feingold, which introduced the Feingold elimination diet to prevent symptoms of hyperactivity.

Numerous studies have been conducted to test this theory since it was realized that Feingold's

recommendations were based solely on anecdotal evidence rather than conclusive scientific evidence. Many studies conducted subsequent to Feingold's have also been shown to be inconclusive, inconsistent, or difficult to interpret for a number of reasons, including inadequacies in study design and scientific flaws.

For example, the European Food Safety Authority evaluated the more recent 2007 Southampton study, a study commissioned by the U.K. Food Standards Agency to investigate whether certain color additives cause hyperactivity in children, and concluded that the Southampton diet provided limited evidence that the mixtures of the food color additives tested had a small effect on hyperactivity in children. However, the effects observed were inconsistent, and there was no way to identify which food color may have been responsible for the effects observed.

Flaws such as these are consistently found in studies attempting to investigate impact of synthetic color additives on adverse behavior in children and do not provide a solid foundation on which to base claims

of adverse reaction related to consumption of these color additives.

Moreover, reports of purported associations between synthetic food color intake and adverse behavior typically fail to acknowledge the large body of pertinent research carried out and published some 30 years ago that failed to find a link.

The National Advisory Committee on hyperkinesis and food additives published a report to the Nutrition Foundation in 1980. According to the committee, studies already conducted by 1980 showed sufficient evidence to disprove the claim that synthetic food colors result in hyperactivity.

Upon reviewing numerous studies on the issue, they found no consistent dramatic adverse behavior in hyperactive children who underwent an elimination diet and then were challenged under double-blind conditions with synthetic food color additives. The committee felt that evidence that synthetic food color additives may produce adverse behavior is uncertain, at best.

Food science and technology make product attributes such as various food colors possible, while

continuing to ensure America's food supply is these safest available. Food companies adhere to safety standards such as the 1960 color additive amendment of the Food, Drug, and Cosmetic Act, which requires FDA premarket approval and safety determination, and, for certain food color additives, certification.

Today, consumers insist upon not only a safe and abundant food supply, but also food products that are convenient, affordable, and have appealing appearance and flavor. Natural and synthetic colors contribute to this capability.

Synthetic colors provide critical stability and coloring power needed to sustain product quality attributes during processing and storage conditions. Color additives can also correct natural color variations or enhance natural colors of food products or provide color to otherwise colorless foods to make them more desirable to consumers.

Consumers or the caregivers choosing to avoid food products with synthetic colors may do so by identifying the presence of the colors in food products via the ingredient lines and avoid a particular

product. Given the rigorous safety evaluation that color additives undergo and the lack of scientific evidence for a link with adverse behavior, IFT's viewpoint is that consumption of synthetic food color additives present no harm to the general population. IFT does support further research in this area to address consumer concerns.

Thank you for the opportunity to present.

DR. ACUFF: Thank you, Mr. Fisher.

Next up is Maia Jack.

MS. JACK: Good morning. I'm Maia Jack, senior manager of science policy at the Grocery Manufacturers Association, GMA. GMA is the voice of more than 300 leading food, beverage and consumer product companies that sustain and enhance the quality of life for millions of people in the United States and around the globe.

The association and its member companies are committed to meeting the needs of consumers through product innovation, responsible business practices, and effective public policy solutions developed through a genuine partnership with policymakers and other

stakeholders.

In keeping with its founding principles, GMA helps its members produce safe products through a strong and ongoing commitment to scientific research, testing, and evaluation, and to providing consumers with the products, tools, and information they need to achieve a healthy diet and an active lifestyle.

GMA member companies manufacture a broad range of processed foods and beverages and import ingredients and export finished products globally. Ensuring the safety of our products and maintaining the confidence of consumers is the single most important goal of our industry. Product safety is the foundation of consumer trust and our industry devotes enormous resources to ensure that our products are safe. GMA appreciates the opportunity to provide these comments in response to the petition to ban synthetic colors based on neurobehavioral concerns.

Regulations must be science-based. GMA is a strong advocate of science-based standards. We agree with President Obama that regulatory decisions must be based on the best available science and ensure its

integrity and objectivity, as stated in the executive order, improving regulation and regulatory review.

It is imperative that new scientific data and findings be reproducible and the findings valid, reliable and meaningful for human safety assessment. To that end, the science underlying the reported association between all six of the color additives and potential neurobehavioral effects in the Southampton study has been thoroughly evaluated by the major safety bodies globally. These expert evaluations include the European Food Safety Authority, the U.S. Food and Drug Administration, Food Standards Australia-New Zealand, United Kingdom Committee on Toxicity, the German Federal Institute of Risk Assessment, the Panel on Food Additives, Flavorings, Processing Aids, Materials, and Contact with Food and Cosmetics of the Norwegian Scientific Committee for Food Safety.

For example, the EFSA opinion on the Southampton study concluded that it contained several weaknesses and that there was no reason to change the official position that these additives are safe for use.

In its recent reevaluation of color additives like we heard earlier today, EFSA decided to lower the ADI of, for example, sunset yellow, not due to neurobehavioral concerns, but rather to possible reproductive concerns. In spite of this finding, EFSA reiterated once again that the data in the Southampton study did not substantiate a causal link between the individual colors and possible behavioral effects.

We wish to point out that only three of the six color additives studied by the Southampton researchers are permitted for use in the USA, sunset yellow, tartrazine, and allura red.

Regarding the World Trade Organization commitment to scientific integrity, the U.S. is a signatory to the WTO agreement on sanitary and phytosanitary measures, the SPS agreement. This international treaty requires that members shall ensure that any sanitary of phytosanitary measure is applied only to the extent necessary to protect human health, is based on scientific principles, and is not maintained without sufficient scientific evidence.

The SPS agreement also requires members to

base their sanitary of phytosanitary measures on international standards, where they exist, and specifically recognizes standards for additives and contaminants established by the Codex Alimentarius Commission.

Countries may do their own risk assessments and establish their own safety standards if necessary to protect their citizens provided that the approaches are consistent with Codex principles. The WTO commitment ensures that food safety policy decisions are founded on globally recognized and accepted scientific principles and approaches to safety evaluation, risk assessment, and risk management.

Codex was established in 1963 as part of the United Nations' Joint Food and Agriculture Organization, World Health Organization Food Standards Program to develop food standards, guidelines and codes of practice in order to protect consumer health, ensure fair practices in the food trade, and promote coordination of all food standards, work undertaken by international governmental and nongovernmental organizations.

Codex standards for food additives and contaminants are based on risk assessments performed by the joint FAO/WHO Expert Committee on Food Additives, JECFA, and reflects safe use levels. JECFA evaluated all these colors previously and are in the process of reevaluating some of them again.

Food safety expert bodies around the world continue to evaluate and reaffirm the safety of synthetic colors tested in the Southampton study or revise the health-based guidance value as appropriate and find no causal link between these colors and neurobehavioral effects. These expert bodies provide health-based guidance values when appropriate, and in doing so, consider all the available science, including exposure based on food consumption data from the U.S. and other countries.

GMA welcomes the comprehensive and in-depth reviews of the evidence now ongoing at FDA and ILSI.

Thank you.

DR. ACUFF: Thank you.

Keith Ayoub?

DR. AYOUB: Good morning. Thank you for

giving me the opportunity to present my comments. I'm Dr. Keith Ayoub, associate clinical professor of pediatrics at the Albert Einstein College of Medicine in New York. I'm also director of the nutrition clinic at the Rose F. Kennedy Children's Evaluation and Rehabilitation Center at Albert Einstein College of Medicine, which is a diagnostic and treatment center for children with special needs, where I've maintained a clinical practice for over 25 years. It doesn't help with voices, though. Pardon me.

Part of my work with children with special needs includes children with attention deficit hyperactivity disorders, or ADHD, and for many years, the issue of colorings and ADHD was below the radar, to some degree, at least in the public eye. It resurfaced in 2007 largely as a result of the Southampton study that suggested some children may be high responders to the artificial colorings in foods.

This received obviously a lot of public attention, and I do feel there's a certain amount of misinterpretation from the study in the popular media that I would like to at least address in the interest

of clarity and accuracy.

Two age groups were studied, the 3-year-olds and the 8- and 9-year-olds; but according to the authors, the younger children were given two doses of coloring, with the higher dose being equivalent to an amount of coloring that would be found, according to the authors, in two 56-gram bags of candy, or a quarter pound of candy total, and the 8- and 9-year-olds were given an amount of coloring that would be found, by the authors' estimate, in four 56-gram bags of candy, or about half a pound of candy.

At first glance, it seemed that the coloring was more associated with hyperactivity than the placebo was. But when the groups were adjusted for the factors such as the week during the trial, the level of maternal education or their pretrial diet, their global hyperactivity aggregate scores in the pretrial week, which were significant factors to adjust for, then a different picture emerges.

The older children were more likely to exhibit symptoms at the highest dose of coloring, but the younger children were more likely to show symptoms at

the lowest dose of coloring. And these results are a bit inconsistent with what one would expect if colorings were truly the responsible agent.

I'm not saying they weren't. I'm just saying that this was an inconsistency that I found very troubling. The authors even concluded that there were substantial individual differences in response to the additives.

Now, as a pediatric nutritionist, I don't have any particular need for kids to be obtaining these colors, I really don't. Many of the colors are supplied in the types of foods and beverages that really should be offered only occasionally anyway.

When I first read the study, I immediately thought that if a parent came to me with a 3-year-old who was eating a quarter pound of candy a day or an 8-year-old who was eating half a pound of candy a day, my first conclusion would be that coloring is not this child's main problem.

[Laughter.]

DR. AYOUB: Proper diet, proper parenting is a bit more the problem. I mean, half a pound of candy a

day for an 8-year-old, I said, "I don't really care what's in it. Stop right there, we've got work to do here." And taking the coloring out of these foods or simply substituting a natural color isn't going to make them more nutritious. These colorings don't particularly add any nutrition, but if you take them out, it doesn't add any nutrition either. Getting children to eat and drink fewer empty calories makes a diet more nutritious and doing that is where I put my priority. Just banning the colors from an unbalanced diet just produces an uncolored diet that remains unbalanced.

All this said, there is, to me, some legislation that might very well help improve children's behavior in the classroom into which I would happily throw my full support. Dr. Romina Barros, a colleague of mine and developmental pediatrician at our center, published a paper a couple of years ago in Pediatrics. This is beyond the purview, but I think it's important for you to understand.

Among 8- and 9-year-old children, the same age group in the Southampton study, having at least a

15-minute period of recess daily was associated with better teachers' ratings of classroom behavior. I think it's important to at least consider other factors that might be affecting children's behavior.

I would feel strongly that mandating daily recess in grades 1 through 6 and mandating daily physical education in grades 1 through 12 would be a huge step in reducing the prevalence of ADHD diagnosis in children. It also seems to be a more meaningful step to addressing the problem, as well as helping address childhood obesity, and frankly, it would make my job a whole lot easier, and a host of other children's health issues.

As for colorings, these foods would automatically be reduced if children simply ate a more balanced diet.

Thank you for your time, and I would be happy to answer any questions you have.

DR. ACUFF: Thank you.

Next up is Dr. Maureen Lamm.

DR. LAMM: Good morning. My name is Maureen Lamm, and my husband and I started a company in 2008

called Mom's ABCs to educate parents about artificial food colorings.

Thank you for the opportunity to take part in this hearing and for the genuine interest and attention you've given to this most important topic.

I'm a physician, board-certified in family medicine and urgent care. I've been practicing medicine for over 15 years and have treated thousands of patients in the primary care and emergency room settings. I am also a published researcher, and my work experience includes research on inner hemisphere cooperation of the brain and testing various Alzheimer's medications.

My most challenging job, however, has been that of a mother. I have three children, ages 5, 7 and 9, and I'm here to tell you that Red 40 made my life as a mother next to impossible.

About five years ago, when my oldest son was 4, he became a real challenge. For the first four years of his life, he was the most laid back, well behaved, and even-tempered child. He's the perfect example of a child from the general population. But

around the age of 4, he started to develop these bursts of aggressive hyperactive behavior that were difficult to manage. He would run around fearless and uncontrollable, even working up a sweat. He was unable to listen, incredibly difficult to discipline, and he seemed incapable of controlling himself.

This behavior was so out of character for him that I knew something had to be wrong. What I started to notice is that on certain days, days when I would give him a children's multivitamin, the number one recommended by pediatricians, or fruit gummies, he was especially difficult. I began reading all the ingredients of anything put into his mouth, multivitamins, gummies, toothpaste, cinnamon rolls, breakfast cereals, cookies, and cakes. The ingredient Red 40 kept popping up.

So I did what any good scientist/doctor/mom would do, and I started to research Red 40. I'm not exaggerating when I say that I was completely shocked to learn that scientists and physicians have suspected this link for over 30 years. There was even a foundation, the Feingold Association, totally devoted

to this very cause.

Why hadn't I ever heard of this link between artificial food colors and behavioral problems? I had to figure it out the hard way. Even my own pediatrician failed to mention this when I went to her about the problems we were having with our son. She referred him on to psychiatrist. My son's behavior strained every aspect of our family life, and we were emotionally and physically drained.

After obtaining educational materials from the Feingold Association, we took action. Like these other moms here today, we cleaned out our pantry, cleaned up our diets, threw away bags of food, and managed to significantly reduce the artificial colors from my son's diet.

Shortly thereafter, we started to see glimpses of our content, laid back son. His face brightened, his eye contact improved, and for the first time in a very long time, he appeared calm.

Since then, over four years ago, we have refrained from all artificial colors and have been testing this theory in our own home. Yes, there have

been occasional dietary slipups, candy from school, cake at a birthday party, when we are reminded unequivocally of the defiant, difficult behavior that results when my son consumes artificial food coloring.

I am here today not for me or my family, but for all those children who are like my son. I urge the committee to protect the health of our children, recommend removal of all artificial food colorings from our food supply.

To put it quite simply, we don't need them and we as a society have so much to gain from their removal. Can a child's consumption of synthetic color additives adversely affect his behavior? Absolutely. I know, because I lived it.

Thank you.

DR. ACUFF: Thank you, Dr. Lamm.

Carolyn Jeletic has an announcement.

MS. JELETIC: A couple of members I understand, because we're behind schedule, haven't been able to check out before the deadline, and the hotel has extended it until 2:00. So just to make sure you're okay.

Okay. We can continue.

DR. ACUFF: Okay. Thank you.

Jorma Takala. I'm sorry. I probably butchered that name.

MR. TAKALA: I'm Jorma Takala. I'm affiliated with no one, so I don't even know what I'm going to say now. I'm going to just shoot from the hip.

My mother told me I started crying when I was 3 years old, and I think that's when I had my first migraine headache. And I basically suffered through behavioral disorders, learning disabilities throughout my entire life, and I self-diagnosed bipolar manic disorder and Asperger's syndrome. In 2006, I started making eye contact with people, and I couldn't do that before.

Basically, what I did is I ended what started out in the '60s. I was kicked out of my elementary school, evaluated, and the doctor tried to tell my mother that I was a sociopath, which I'm not. And so in 2006, I went to the hospital with a type II diabetes condition, a 500 glucose blood level, and I felt like I was going to die. And I had no insurance and no means

to take care of myself with any medicines or doctor visits. And so I did the only thing that I could do, which was change my diet. And at that point, I discovered that I have an acute allergy to all of the artificial colors, and it's not just foods, because the documents that I -- the handout that you guys have, if anybody saw that, the top page is from the Environmental Protection Agency. And under toxicity, it says that the Azo compounds are acutely toxic by any route of exposure, which means foods, drugs, cosmetics, toiletries.

I got a migraine headache from taking Excedrin.

[Laughter.]

MR. TAKALA: And it's ridiculous, but they use blue dye in the white pills, because the blue actually tricks the eye and makes things look whiter.

Ultimately, with all of these additives and everything, I figured out that it's pretty much -- I think I'm the only person who could stand up here and say that it's the cause of autism, and the mechanism through which that occurs is the migraine headache. It

causes a pinching of the cisterna magna, and the fluid pressure actually builds in the skull, which causes a hypoplasia or arrested development of the brain, specifically around the brain stem, where the hippocampus and the temporal lobes are at, which are specific to the autism problem. And that's pretty much it.

My Facebook page has all kinds of information links and documents from all kinds of different places that support this, and I guess I'm done. Kind of nervous and stuff.

Thank you.

DR. ACUFF: Thank you, Mr. Takala.

Next up is Karen-Lynette Bauer.

MS. BAUER: Hi. I am myself a primary care practitioner, but not in Western medicine. I practice oriental medicine in the State of New York. I come from a long line of doctors. My great-grandfather was a professor of science in the medical school at the University of Berlin. My father is a doctor, my brother is a doctor, and, interestingly, when I called him to tell him last night that I was here about to

testify before the FDA about food dyes in food, he said, "It's about time." He's an ER doc. He's not some alternative guy.

I'm here to talk about my personal experience with food dyes. It might be a little embarrassing for me, but I am going to tell you this, because I think you need to know how serious the experience is from the inside.

I didn't discover that I had a response to dyes until I was maybe 35-40 years old. I had developed allergies to many foods and chemicals and airborne allergens about when I was in college, and I started doing elimination diets. I saw Theron Randolph at the hospital in Chicago, where they isolate you and test you one-by-one. They do a washout period and then test you on things one-by-one in a completely sterile environment. Very interesting. I had a lot of allergies.

So I very carefully document what I eat, what I'm exposed to. I trace things back. I experiment. I repeat my experiments until I know for sure what I respond to, because if I don't eliminate these things

from my life, I am extremely ill.

So how I found out about the Yellow Number 5, I had been doing some reading in a book about a doctor who was an allergist and discovered some interesting things in his patients about food additives. And so I decided to try for myself. I found out about Feingold, as well. And I eliminated food dyes from my diet completely, eating just pure food that I could make myself and, therefore, I knew it didn't contain any colorings.

I chose organic foods, because I understand foods like oranges are sprayed with dyes as well, to make them brighter. So I was quite careful, and what I discovered was within 24 hours of ingesting either a beverage, bottled beverage that had Yellow Number 5 or pickles, which always contain Yellow Number 5, I would have a two-hour period of suicidal ideation. Me.

I have an honors degree from Stanford. I have had a delightful career as an opera singer for over 20 years. I now have a career I love as an oriental medical practitioner. I am not some depressed, sad, poor, pathetic thing. I am in love with life. I love

sports, I love music, I love art.

But when I ingest Yellow Number 5, if I just take the tiniest little fraction of a pickle, for two hours, the world is at an end for me. I have no value, I can't do anything, the world is horrible, I feel like committing suicide, I hate myself. Two hours later, it's gone, and I'm fine again. I'm my ambitious, arrogant, opinionated self again, in love with the world.

Now, you may find this hard to believe. It's not in a scientific study. This is simply repeatable clinical, personal experience, and I have repeated this experiment at least 30 times. I don't do it anymore because I don't want to feel like that. But this is an absolute correlation. There is no other explanation for this. I eliminate this from my diet and if I have any food containing it -- and, you know, in a beverage, how much can there be? These are just very pale yellow -- you know, it's the very tiniest bit of a color, and I still have the same response.

So I want you to know how bad it can be. And in a child, I had these experiences as a child; I just

didn't understand them. I used to go into my closet as a child, cover myself with clothes, and just hit myself because I hated myself so much, and then it would be gone.

How do you think a child -- what kind of response can a child have to that? How do they understand that about themselves? As an adult, I have ways to understand, to reason, to think about that, to put it in a frame and say, "That's not me. That's a chemical that's affecting my brain."

But children do not have that ability and it is your responsibility as a consumer protection agency, not an industry protection agency, to protect consumers from products that do them harm. I'm not claiming that everyone has that reaction, but enough children do. If you prevented one suicide by getting rid of artificial colors, it would be worth it.

DR. ACUFF: Thank you.

Betty Douglas?

MS. DOUGLAS: Thank you for this opportunity to share my family's experience with food dyes. Throughout elementary school in Arlington, Virginia in

the 1970s, our daughter, Kim, was a very good student. She made As and Bs and the teachers' comments were consistently positive. She did, however, exhibit some behavioral problems at home. She would have frequent tantrums. She would easily anger, slam doors in exaggerated frustration. In addition, she had a short attention span, and she had trouble remembering complex verbal instructions.

When Kim was in the fourth grade, her teacher began reporting that she was not paying attention in class, and her grades began to decline. She was eventually diagnosed as having a learning disability called auditory memory deficit. Kim was unable to remember verbal instructions or information that was heard rather than read. The school psychologist said that her learning disability was very severe.

The following summer, I happened to read an article on the use of the Feingold diet for children suffering from learning disabilities. The children described in this article who had been helped by putting them on the Feingold diet sounded exactly like Kim, the learning disabilities, the behavioral

problems, the short attention span.

So I joined the Feingold Association of the U.S. and received their safe food list and, with the support of our pediatrician, began the diet in the summer of 1980. About five days into the diet, we saw a dramatic change in Kim's behavior. The tantrums and angry outbursts ceased. They just stopped.

After several months on the diet, when we tried adding back into her diet foods with artificial dyes and flavoring, the behavioral problems returned. It would take two hours for the offending additive to have an effect on her behavior. We could time it.

When Kim was in the sixth grade, I asked the school psychologist to give her the same auditory memory test that had been given to her two years before, before we had put her on the diet. The psychologist reported that Kim showed absolutely no evidence of a learning disability.

Dr. Feingold's thesis was that in some people, food additives actually cause a learning disability and behavioral problems, not just exacerbate them. He believed that additives caused a kind of short-

circuiting in the brain that causes various brain functions to be disrupted. Children often exhibit behavioral problems when they are sick, because children's medicine is highly colored and flavored. Through the years, I would ask her doctors to prescribe prescriptions for uncolored and unflavored medicines.

Because of the laws in this country that govern food labeling, one cannot rely on simply reading the labels to know the ingredients of a product. Food processors indeed only list the ingredients that they use, for example, strawberries, not the hidden ingredients, such as the red dye that was previously added to the strawberries.

Kim was on this strict diet until she went to college. Throughout her adult life, she has been on a modified Feingold diet, and I brought her with me today and I'd like to recognize her.

Kim, would you stand?

Kim is now 40 years old. She's married, with two children, and she lives in Fairfax County, Virginia. Her 4-year-old son, Jack, began exhibiting the same problems as Kim when he was 2 years old. He

has now been on the Feingold diet for over a year. He has had the same dramatic reaction to having additives removed from his diet.

The Feingold diet has enabled our family to protect two children over a span of 30 years from the artificial dyes and flavoring that permeate our food supply and have caused them behavioral problems and learning disabilities.

One final note. In the mid 1960s, my husband and I lived for three years in Geneva, Switzerland. Soon after arriving there, I discovered that I could not purchase food coloring in the stores because it was banned in that country. I had to ask my mother who lived in the States to send me food coloring so that I could decorate Christmas cookies. The Swiss knew 50 years ago that food dyes were unsafe. Isn't it time that we acknowledge the same?

Thank you.

DR. ACUFF: Thank you.

Dave Schoneker?

MR. SCHONEKER: My name is Dave Schoneker, and I'm director of global regulatory affairs for Colorcon,

Incorporated. Colorcon is a world leader in the development, supply and technical support of formulated coatings, inks, pigments and other ingredients used in pharmaceuticals, dietary supplements, and in the food industry.

Colorcon appreciates the opportunity to provide comments to the FDA Food Advisory Committee on the topic being discussed today. We've submitted our written comments to the advisory committee last week, which includes significant detail regarding the safety and the technological need for synthetic colors for various food, dietary supplement, and pharmaceutical applications.

Colorcon has significant experience using both synthetic and non-synthetic, so-called natural colors. Therefore, we can provide significant input concerning both the safety of synthetic colors and the significant problems that exist when trying to substitute non-synthetic colors for synthetic colors in many types of applications.

The use of non-synthetic colors as substitutes for FD&C colors simply is not feasible in many cases,

as is outlined in our written comments. I suggest you take a look at those.

I'd like to use the rest of time, however, this morning, since it's very limited, to focus on information we received from an expert in the field with real clinical experience working with many ADHD children every day.

Colorcon requested Dr. Donna Antonucci to comment on the effects of synthetic colors in the diet of children of various ages in view of her greater than 20 years experience in treating children with ADHD.

Dr. Antonucci is a pediatrician who is certified as a diplomat in the American Board of Pediatrics and a diplomat of neurodevelopmental disabilities. She's an affiliate of the Department of Pediatrics of the Children's Hospital-Philadelphia, and the community medical staff at Dr. Christopher's Hospital for Children in Philadelphia. Dr. Antonucci is also a medical director of her own neurodevelopmental pediatric and adolescent practice.

Dr. Antonucci provided a letter and a statement which she asked that Colorcon present both

orally at this FDA public meeting, since she cannot be here, and also in our written comments, which was submitted, as I mentioned, last week.

In her statement, Dr. Antonucci provided the following opinions, and this is direct from her statement that's been submitted. She said, "The role of diet in the onset of exacerbation on hyperactivity and behavioral issues has been discussed for years and remains somewhat controversial, since evidence exists both to support and to refute the effect of different dietary agents. However, in my clinical opinion, from personal medical experience and review of the literature, the evidence is much stronger to refute the food color additive and elimination diet, such as the Feingold diet.

I've treated many ADHD children in the past 20 years, and I treat a lot of my patients from the time they are very young to the time they are young adults, and, frankly, I just haven't seen any connection between the presence of food colors in a diet and any increase in hyperactivity in these children.

I recall only one case many years ago where a

dye used in a drug formulation caused a problem. Hyperactivity, however, was not the problem for that child, but rather ineffectiveness of the medication.

Accordingly, in my clinical practice, I do not support or recommend any elimination diet unless there is some type of special circumstance, which is very rare. Certainly, a healthy, well balanced diet is of paramount importance to a growing and developing child, but food colors and food additives are not the major cause of hyperactivity in children.

A review of scientific evidence has found only a minority of children were actually affected by what they eat, and a combination of genetics, brain function and environmental toxins, such as smoking or drinking alcohol during pregnancy, are more likely to be involved with the etiology of ADHD, with no single factor to blame.

Neither my own clinical experience nor the scientific literature support that FDA should take any specific action to control the food color additives in the McCann report, other than to require that the specific food color present in the product be listed as

an ingredient on the product label, which has already been required for years.

This would allow the small portion of the population who might potentially be sensitive to these colors to know when the color is present and they can certainly avoid consuming the product if they so desired.

Clinically, I have not observed any demonstrated connection to significant problems with hyperactivity with children which would warrant any type of special warning label requirement concerning hyperactivity or any justification for removing these safe colors from the market." And that's from her statement.

I'd just like to finish by saying Colorcon applauds the FDA for using a scientific approach and for its initial response to the CSPI actions, indicating that there is no significant causal link to hyperactivity in children.

Currently labeling practices should suffice to allow consumers to make whatever choices they want regarding these colors. We are hopeful that good

science will prevail in these discussions as they go forward, and Colorcon certainly supports that, and that FDA and this committee will not revert to simple precautionary thinking based on the very limited supporting data presented at this hearing so far that is specific to any particular food color.

Thank you very much.

DR. ACUFF: Thank you.

Our final public speaker is Eric Hentges.

DR. HENTGES: Well, good afternoon now. I'm Eric Hentges. I'm executive director of International Life Science Institute's North American branch and I appreciate the opportunity to provide comment to FDA.

ILSI North America is a public, nonprofit foundation that actively collaborates with government and academia to identify and resolve scientific issues important to the health of the public. ILSI North America's programs are supported primarily by its industry membership.

In collaboration with the Life Sciences Research Organization and Dr. Joel Nigg, an ADHD expert at Oregon Health and Science University, available

scientific evidence was reviewed. Detailed findings will be published in a peer-reviewed meta-analysis manuscript, and I will present the preliminary analysis today.

Our literature search identified 53 human studies. Studies were graded for relevance and usefulness. The main focus of the analysis was on studies that conducted a double-blind, placebo-controlled challenge trial using synthetic color additives. Thirteen of 16 identified studies yielded effect sizes, and eight were relevant to gauging the percentage of children affected within the sample selected.

In summary, these studies yielded uncorrected weighted effect sizes of D equals .33, which was statistically reliable. But the effect was not reliable in observer and objective test ratings when those were obtained. It was observed only in the parent ratings, which tend to show larger effects.

The authors noted several limitations within the literature that warrant consideration. The children who react to dyes generally react to other

foods. Food restriction appears to help some children, but it remains unclear whether removing dyes alone will benefit these children.

When children are preselected by reported response to an elimination diet, a behavioral response to dye challenge is observed in as many as 60 percent, and it is limited, again, only to the parental ratings and was not observed by teacher or clinician ratings. There are two well-designed population-based studies, but neither provide enough information to gauge the percentage of children responding.

A number of the large community studies, there were confounding food components along with the synthetic food colors. Therefore, it is impossible to determine the effect, if any, that could be attributed to synthetic color additives. And lastly, as noted previously, the effect was seen in parent ratings and the meaning of that is unclear.

In conclusion, based on our analysis of the literature, pooled across available studies, no significance was detected in double-blind, placebo-controlled studies for observer and objective test

ratings and only for parent ratings was a reliable non-zero effect detected.

The effects observed in community studies are confounded by inclusion of other food components, leaving it unclear how much of the community effect is attributable to FDA-approved food dyes. It is premature to make conclusions for causal associations regarding specific FDA-approved food colorings in ADHD.

Future research should be pursued to address mechanistic pathways and mode of action, as well as clinical effects above a meaningful threshold. A review paper was recently accepted by the Journal of Pediatrics, and in this paper, they will address diet and ADHD methodology, and this could be helpful to enhance the design of future studies.

Thank you.

DR. ACUFF: Thank you, Mr. Hentges.

Okay. We have an opportunity for committee members to question any of the public speakers, if they would like. Dr. Freeland-Graves?

DR. FREELAND-GRAVES: The last speaker, did he use the number 53 human studies?

DR. HENTGES: Correct, and those are attached. Those studies are attached as references to the handout.

DR. FREELAND-GRAVES: Okay. And the FDA reviewed 33, is that correct?

DR. HENTGES: Yes.

DR. FREELAND-GRAVES: What happened to the other 20?

DR. ACUFF: I'm sorry. I think you need to use the microphone.

DR. HENTGES: Yes. Those were looked at and considered not to reach the standard of review for this analysis.

DR. ACUFF: Additional questions?

[No response.]

DR. ACUFF: Okay. Thank you very much to all the public speakers. We appreciate your time and especially travel to come speak to us today.

We're going to break for lunch. We will take 40 minutes. So we'll start back here at 1:10.

(Whereupon, at 12:32 p.m., a lunch recess was taken.)

DR. ACUFF: I think we have everybody back.

All right. We are about to begin the discussion and response to questions.

If you look in your notebooks under tab 4, we have the charge to the committee that was put forth by FDA and the questions that they would like for us to answer. There are five questions within our voting. You saw that some of those were split, so we'll deal with that as we get to them.

First of all, let me say that the plan is to discuss the questions and we need to hear your input, certainly. We'll follow the same format that we have during the presentations, where, if you will catch Carolyn's eye, then she'll keep a list of the names so that I can call them out in order, and then I will recognize you, so that we have all that for the transcript.

It's also I think important that we recognize the transcript is as important as the vote. So please make sure that the things that you say or things that you want to say are put out there so that they are included in the transcript, because FDA will refer to

that as much as the vote in the final decisions that they would make.

Also, just to make sure you know, we do have resource people here from FDA. So if we have toxicology or exposure assessment questions that we might want to ask, we have people we can ask that about. If we have legal questions, we have people that we can refer to there. So if that's the case, just let me know that that's something you'd like to discuss or need some additional information on, and we'll make sure that the right person is tagged to help us.

Does anybody have any questions or concerns before we get started? Let me read the charge and then we'll do that.

You see on the PowerPoint slide up above, the task before this Food Advisory Committee is to consider available relevant data on the possible association between consumption of certified color additives in food and hyperactivity in children and to advise FDA as to what action, if any, is warranted to ensure consumer safety.

Specifically, there are several issues for

which FDA would like feedback from the committee, and then we have the five questions.

DR. VOORHEES: A slight problem with the wording, where it says "in hyperactive children." Isn't it supposed to say "in hyperactive children and other problem behavior?" It appears in some sentences and not in others, but I thought Dr. Cheeseman indicated that that was, in fact, intended to be included.

DR. ACUFF: Right. Dr. Voorhees, that's something we do need to discuss.

Dr. Cheeseman, can you address that?

DR. CHEESEMAN: As I said yesterday morning, I think to the extent that that issue is covered in the review that has been presented, I think it's legitimate for conversation. I don't know that it necessarily requires a change in the charge. It is in the record, and now twice in the record.

DR. ACUFF: Ms. Lefferts?

MS. LEFFERTS: I was going to propose just two changes to this charge based on Dr. Cheeseman's earlier remarks and based on other things we've heard, and that

would be to add, where it says "hyperactivity," to say "or other adverse effects on behavior," because I think that's what we've been hearing about.

Then the other change that I would really like to see in this charge is where it says "and to advise FDA as to what action, if any, is warranted to ensure consumer safety," we were made aware of the legal framework in which FDA is acting and that our advice has to be within that framework.

I think it would be very helpful to change the charge slightly to say "and to determine if there is convincing evidence that establishes, with reasonable certainty, that no harm will result from the intended use of certified color additives only with respect to possible effects on behavior and to advise FDA as to what action, if any, is warranted to ensure consumer safety."

So that would be just to add that legal clause, understanding, as Dr. Cheeseman had said yesterday, that we're only looking at a portion of the body of evidence. But I think it's important to include this, because it might change how different

committee members would respond.

I think it's important. It's one thing when we're looking at things with the most narrow lens and it's another thing when we're looking at this legal standard of convincing evidence that establishes with reasonable certainty that no harm will result.

DR. ACUFF: Dr. Cheeseman, can you advise us on our charge?

DR. CHEESEMAN: I think the last suggested change is problematic because you're only looking at a portion of the information that we would consider in making that ultimate determination. A lot of the discussion today has been around the rigor, for example, of the exposure assessment, and you in fact have not been offered a rigorous exposure assessment.

Any safety assessment going forward would require that. And so I don't think you have adequate information to in fact address that charge. And so that was not the charge that we gave you for that very reason.

DR. ACUFF: Regarding the first suggested change, though, Mitchell, is that an issue?

DR. CHEESEMAN: As I said earlier, I don't know that it's necessary, but I wouldn't offer any objection to it.

DR. ACUFF: Okay. What does the rest of the committee think about that? I think the first change we can do if we want to. The second one, not.

Dr. Castellanos?

DR. CASTELLANOS: I would support making explicit that we're talking about hyperactivity and behavioral problems in children, in part, because the term "hyperactivity" is vague enough that, on the one hand, we could argue that it includes other problematic externalizing behaviors, but it's probably better to be explicit about it.

DR. ACUFF: In agreement? All right. So we will make that change to read "hyperactivity and" --

MS. LEFFERTS: "Or other adverse effects on behavior."

DR. ACUFF: All right. So let's go to the first question then.

In the review of published research presented in the overview and evaluation of proposed association

between artificial food colors and attention deficit hyperactivity disorders, ADHD, and problem behaviors in children, studies were evaluated based on the criteria described in part 3 of the review.

Were these review criteria appropriate in the evaluation of these studies? Should the criteria be modified in any specific way; and, if so, how? And what is the basis for the committee's recommendation? And are there other criteria or studies that should be considered; and, if so, that is the basis for the committee's recommendation?

So we have multiple questions to discuss within this question. And I would say probably the best way to proceed is just discuss the issue, and when we feel like we've discussed it to the point we can't discuss it anymore, we'll vote. And that would be page 57 of the review.

Dr. Voorhees?

DR. VOORHEES: So I'm going to say yes and no. I think some of the criteria that they used in evaluation under section 3 were appropriate, but my area of concern is that we're talking here about the

developmental effects of these compounds on brain development and behavior. I do not believe that the tests done, including the two-year rodent bioassays, provide a sufficient basis for determining a noael in the contest of the present discussion, and that is what it is in section 3.

In determining ADIs in relation to EDIs, those margins are based on studies that do not appear to me to be appropriate for setting that kind of a safety margin. If we say hypothetically that a two-year bioassay in a rodent is insensitive to developmental and neurobehavioral effects, then those making those safety determinations based on those data misestimate what the safety margins are.

Since the FDA bases ADIs on noaels from two-year rodent bioassays, there is a significant risk that the ADIs are set too high. In FDA's table comparing ADIs to EDIs for the high consumer, which in the current context is a means of estimating the high consumer children, the EDIs for Red 40, Yellow 5 and Yellow 6 are closely approaching the ADI for a 30-kilogram child. This means that for at least three

of the certified color additives, estimated EDIs are near the threshold for reaching a significant level of concern about these food additives' safety.

Should the ADIs currently in use be too high because they are based on data that does not reflect developmental additive exposure, and nor do they include outcome measures of behavior, then there could be significant risk that the ADIs are erroneous, they're incorrect, and may actually exceed these values. And the safety margin set of 100 also may be not adequate for the protection of infants and children or, for that matter, although it's not directly being discussed here, in utero exposure.

DR. ACUFF: Dr. Jones?

DR. JONES: I understand what you're saying, but this is a very, very narrow question, and trying to separate out sort of a discussion about the results or the findings, which will be later the criteria by which they're assessed, what bullet -- can you just tell me how you would change the bullets on page 57? I mean, that's what we're discussing.

DR. VOORHEES: (Inaudible - off microphone).

DR. JONES: Tab 7 in the report and, specifically, the question is the criteria for review. It has nothing to do with the results.

DR. VOORHEES: (Inaudible – off mic.)

DR. JONES: I guess just for my edification, can you show me which criteria and tell me what the suggested change is?

DR. ACUFF: Dr. Voorhees, I think that maybe your comment might be more appropriate for question number 5.

DR. VOORHEES: (Inaudible – off mic.)

Dr. Gray?

DR. GRAY: Thank you. What I think is important about having these criteria -- I think that they seem quite reasonable. What makes them valuable to me is simply the fact that they are there and made explicit, so that we know, as FDA went through this review, what it is that they looked for in each of the -- both for inclusion into their review and then the standards that they used in evaluating.

So as I look at it, I see no real problems. I think they're appropriate. One thing that I would have

liked to have seen, but it may have been outside of the scope of this, is an attempt to look for criteria in evaluating the body of work, not each individual study. That was something that would have been helpful to have a view done under very rigorous and explicit conditions to look at the whole body, not each individual study.

But as this looks, I see no problems with the criteria that were chosen.

DR. ACUFF: Dr. Vugia?

DR. VUGIA: Thank you. I just want to say that I think the intent of the question is really focusing on the review of the clinical trials. So we're focusing primarily on the human trials that were reviewed here in-depth, although I do agree with Dr. Voorhees about the animal studies that need to be done. I think it is somewhat slightly different in terms of the focus.

Just on that, I do agree with the criteria there, listed here.

DR. VOORHEES: Let me correct what I said. To the extent that we're talking here, specifically in response to your question, about the clinical studies,

I do agree. That was the yes part, which I didn't expound on, on which I agree that those criteria are appropriate.

DR. ACUFF: Ms. Lefferts?

MS. LEFFERTS: I'm concerned with these criteria. The size of the study, the doses used, the time between exposure and outcome are not identified as criteria here, and I think those are very important criteria to use when evaluating the study; not to exclude studies, but to take that into account, because it can influence a type I or a type II error.

DR. ACUFF: Any other comments on the criteria? Dr. Fenner-Crisp?

DR. FENNER-CRISP: Just one that would extend Dr. Gray's comments. I, too, would have liked to have seen a more robust treatment of the body of evidence as a whole, in addition to the study-specific evaluations that were done by these criteria.

Yesterday, Ms. Lefferts raised the issue of incorporating the Bradford Hill criteria concept into this evaluation process, and I would suggest that they would be most appropriately applied in a weight of

evidence evaluation that I think is critical to have accompany the study-by-study evaluations before final decisions and memoranda are created.

DR. ACUFF: Dr. Jones?

DR. JONES: So I guess to comment on that and Dr. Gray's comment, I agree. Obviously, that would be nice, but that's sort of a whole separate way of doing analyses. I don't think it was the charge of this contractor. And, in effect, the discussions that we had about the meta-analyses over time, I think one of the attempts -- that was sort of what they were trying to do.

DR. ACUFF: Dr. Fenner-Crisp?

DR. FENNER-CRISP: There is a section at the end of this document that speaks to their overall conclusions, and it's about a page and a half long, which is a whole lot less than the many pages that are study-by-study. So I did see it within the scope of the activity to do something like that.

DR. ACUFF: Ms. Lefferts?

MS. LEFFERTS: Well, of course, I'd like to agree with Dr. Fenner-Crisp, who was agreeing with me.

But, also, I very much see it as we're trying to figure out if there's a link between artificial food colors and behavioral problems in children. So of course we need to look at all the evidence and weigh the evidence. So I think it is very appropriate to have some criteria for doing that and that the Bradford Hill criteria are certainly very useful in that regard.

DR. ACUFF: Dr. Castellanos?

DR. CASTELLANOS: I basically support the application of these criteria, but one of the two that's highlighted as being particularly important is the last one that evaluated whether confirmatory sources of outcome data concurred.

This is highly desirable, without question, but as I mentioned, it certainly doesn't characterize this field, and it's really a conundrum that we have when we do get multiple measures of knowing how to handle them. And do you do multiple statistical tests for each of them? What are your outcomes likely to be?

So in this regard, my sense of how this criterion was applied is that the Southampton study, which set out an aggregated measure that combined

multiple measures in an a priori way, was an attempt to create an index that would depend on that kind of multiple observer perspective.

My sense of the review is that it's seen as failing on that count. And so that's a question I have as to whether or not there isn't a simpleminded application of this criterion that is missing the potential value of that approach.

DR. ACUFF: Dr. Castellanos, do you think, if that were not weighted as heavily in the evaluation that was done and the review, do you think that would have changed the ultimate review outcome?

DR. CASTELLANOS: I'm not sure. I can't say how much that factor was factored in. But I do think that there is an expectation that multiple observers and objective measures should somehow clearly converge. Unfortunately, as I've said repeatedly, that's rarely the case, and so we wind up having to decide basically on the sense of are they at least going in the same direction, whether or not we have a kind of rough confirmation.

DR. ACUFF: Dr. Gray?

DR. GRAY: I don't know these sorts of measurements at all, but if you're getting these conflicting measures, how do you know which one to believe?

DR. CASTELLANOS: It's a big problem.

DR. GRAY: Okay.

DR. ACUFF: I'm told the contractor is here. Would you like for him to address how this might alter the review?

DR. GRAY: That would be excellent.

DR. SOBOTKA: I'm Tom Sobotka. I'm with the contractor, as you all were talking about.

In terms of application of that particular criterion for the McCann study, the one I think that's at issue, actually, I looked at the -- I had access to the final report from that study, the Southampton study, that I had reviewed about a year before I think, this contract -- this overview was done.

So I had access to that information, and that sort of had been factored into my evaluation. So I didn't just look at the aggregate measure as a singular measure. I was looking at the component sources, and

that was what I was sort of basing a lot of my evaluation of that on.

In that component source evaluation, which -- I don't know whether you've had access to that part of the information. In the component source, it was heavily weighted -- I mean, there was a heavy contribution by the parental observations and ratings, and not so much by the teachers or the clinical observations that they had.

This then sort of fit into my criterion of this multiple -- having confirmation from multiple sources. And there really wasn't that much confirmation of multiple sources looking at the individual sources to that aggregate measure that they used.

So that was sort of the basis that I was looking at in evaluating that. And, obviously, as I sort of mentioned several times in that report, we can't discount that, but it doesn't have as much of an impact as if there were some -- the teachers and parents seeing the same thing in the child. And if it was all based on the parents' observations, there's a

question as to what exactly that means; which measure do you take as being the more real, the negative outcome or the one that's heavily weighted?

The aggregate measure, I'm not even quite sure, the way that they calculated that, whether there was any weighting for the different outcome sources, the parents, teachers, clinical observations.

DR. ACUFF: Dr. Castellanos?

DR. CASTELLANOS: In the older children, they used a continuous performance task measure.

DR. SOBOTKA: Yes.

DR. CASTELLANOS: And did that contribute at all?

DR. SOBOTKA: Yes, it did, and that created -- and I think I tried to interject that and the measure in the older children. However, as I think was mentioned, there were some fatigue factor in those observations, and I still couldn't discount that. They still came out to be significant as separate measures. So there is some evidence that there is some effect in the -- there is some treatment-related effect in the older children based on both the parents and the

continuous performance task that the children were undergoing.

No, I didn't discount that, but I did try to include that in my evaluation.

DR. ACUFF: Dr. Voorhees?

DR. VOORHEES: So you looked at the disaggregated scores.

DR. SOBOTKA: Yes.

DR. VOORHEES: As I think you described them in the report. And in the Southampton study, they used the aggregate intentionally, as we heard yesterday, as a way of avoiding a problem of doing too many --

DR. SOBOTKA: Cherry-picking, I think, yes.

DR. VOORHEES: -- or doing too many statistical analyses.

I'm just asking you, when you disaggregate and you start looking at the significance level of each component, you're kind of undoing one of the intents of using an aggregate score up front.

DR. SOBOTKA: Well, I don't necessarily agree, because I don't -- basically, I don't really agree with the idea of the aggregate score in this particular area

of investigation because of the problems with the disparate effects noted by parents, teachers, clinical observations.

If you combine all of those and you have a heavily weighted influence by one of those components, then that's going to be the driving force. So what you're doing is you're just saying that, okay, then we're going to base our evaluation on what the most dominant observation is, and the other ones were just going to basically -- they're going to be subsumed into that.

DR. VOORHEES: If you have an aggregate score in which some components are not contributing to the outcome, they'll work against you.

DR. SOBOTKA: Not unless that one outcome is particularly stronger than the other ones.

DR. VOORHEES: Well, you can't get an effect in the aggregate that is greater -- if you have a lopsided contribution, the aggregate might be bigger than the one contribution, right? That's possible. But it's not going to deceive you.

DR. SOBOTKA: Well, it does if you look at the

aggregate scores, because they did do the statistics on each of the aggregate scores -- no, I'm sorry --

DR. VOORHEES: The disaggregated.

DR. SOBOTKA: -- the disaggregated scores. And you can see that there is a predominant influence by the parents.

DR. VOORHEES: But you got two statistically significant --

DR. SOBOTKA: In the children and in the -- I mean, the older children and the younger children.

There was another complicating issue or an issue in here. There were three basic analyses that they did. They did it on the entire group, and then they did the analysis on just the component -- the group, the children that ate 80 percent more of their -- and then the third group of just the group where they had all of the data intact for all of the -- and that was a smaller group of children.

Now, in the original design, as it's expressed in the description of the methodology, the one analysis, the component types of analysis that would have been the more important one is the one that

included all of the children's data, all of the children, not just the group of children that consumed 80 percent and not just the group for which they had all the complete data.

Whichever one of those types of analyses that you want to select, you can find more significant effects if you looked at one of those than if you looked at the overall group, when you include all of the children in the analysis.

DR. VOORHEES: As you stepped through those from the full data set to the greater than 85 percent to the so-called complete consumption, isn't it the case that the effects looked slightly progressively more?

DR. SOBOTKA: No, not necessarily. They jumped around. There were some -- you're talking about the disaggregated groups. There was some significance that changed in the three different -- across those three different types of analyses. But when you do the aggregate, then it sort of eliminates some of the bouncing around of the statistical significance.

DR. ACUFF: Dr. Jones, and then

Dr. Castellanos.

DR. JONES: I appreciate and think this is an important discussion, but I also think we're getting way off question 1.

DR. ACUFF: Dr. Castellanos?

DR. CASTELLANOS: In terms of the objective test measures for the older children, do you recall the effect size for those effects and were those --

DR. SOBOTKA: Honestly, no.

DR. CASTELLANOS: No?

DR. SOBOTKA: I don't. For the whole sample -- now, for mix A, for the whole sample, it was .1 just for the 8- and 9-year-olds, .1. For the group that had a greater than 85 percent consumption, it was .08. For the complete case, that's where they just had complete sets of data, no missing data in there, that was 0.18. None of those were identified as being significant.

Then in the mix B group, for which the older children were supposed to have been responsive, the whole sample showed no significant effect, and the effect size was .19. For the greater than 85 percent

consumption, the non-significant effect size was 0.2. And then for the complete case, where they just had all of the data and no missing data, it was a significant .31, 0.31, and that was just for the CPT task.

DR. ACUFF: Ms. Lefferts?

MS. LEFFERTS: We've heard how in the DSM, the two settings is in that definition, but we are looking at a broader range of behaviors than just ADHD. And I have understood from the presentations that some of these behaviors are normally distributed in a general population, obviously, where ADHD is at one end of that distribution. But we're also concerned about effects on behaviors that are milder in the general population.

So while it certainly would have added strength to the evidence to see results in multiple settings, I don't think we can put too much weight on that, given particularly the very real challenges in measuring these kinds of effects. It's not like measuring blood pressure; we've already heard that.

If you have a kid who is really extreme and has zero impulse control, you're probably going to see it in multiple settings. But if you're talking about

something more subtle, I think it's very plausible that you are not going to necessarily see it in multiple settings. And, in fact, even it sounds like in the ADHD literature, you don't always see it in multiple settings, much less children that are more subtly affected.

I'm convinced that the aggregate measure used in the Southampton study is really quite robust, and that the presentation we heard about that lays to rest some of those criticisms regarding multiple settings.

So, yes, it would be great to have multiple settings, but let's not put too much weight on it.

DR. ACUFF: Back to the original question. We need to be able to vote. Were these review criteria appropriate in the evaluation of these studies? So they did do a review. They used these review criteria on pages 57 and 58.

Do we believe, as a group, that those were appropriate for conducting this review? And then we can elaborate after that.

Are we at a point where we can vote on that first question? No? Question 1 is part A and part B,

on this, but up there we have part B and C.

Can we go back to part A?

MS. JELETIC: Harold, does the software allow us to vote? Could you advance to the third slide, please?

Okay. And then go to the -- is that the voting? It's sort of cut off. So that's the voting question.

I'm just wondering if we need to finish the discussion on B and C before we actually take the vote.

DR. ACUFF: What do you think? Do we need to continue discussing? Okay, yes.

MS. JELETIC: Thank you. So, Harold, could you go back? Thank you.

DR. ACUFF: Dr. Castellanos?

DR. CASTELLANOS: I apologize for needing clarification, but the last item says that confirmatory sources of outcome data, including testing, are part of the criterion. It's not clear to me from our just concluded discussion whether or not the testing in the Southampton study in the 9-year-old children producing effect sizes, essentially in the same range as those

that are purported for the aggregate measure, was seen as confirmatory or not.

I'd like clarification on that.

DR. ACUFF: He can clarify.

DR. SOBOTKA: If I understand the question, you're talking about the aggregate score or the --

DR. CASTELLANOS: No. What I've heard is that the parent --

DR. SOBOTKA: The individual.

DR. CASTELLANOS: The parent scores were suggesting an effect of the food additives and sodium benzoate, and the effect sizes of the continuous performance task, again, vary between .1 and .3, depending on how the data were cut, which is essentially the range in which we've been told that the effect lies, at about an average of .2.

I think that that's a separate question of whether .2 is something that we believe is meaningful, but I'm wondering whether you saw this as adding confirmatory weight to those results or saw that they were not strong enough because they didn't reach significance.

DR. SOBOTKA: When I was looking at this, I viewed the whole sample as being the group that was the basic analysis for the study, because I read in the methodology that this was the signal group, the sample.

So looking at the whole sample for the 8-year-olds, 8- and 9-year-olds on mix B, there were -- and, again, just based on statistical changes, there were statistically significant effects for the whole sample in the parents' ratings at 0.13, was the effect size. There were no significant changes in the teachers' classroom observation or the CPT test in the whole sample for that mix B for the 8- to 9-year-old children. So the only significant effect there, based again on statistics, was just the parents' observation.

But if you jump over to the complete case, the parents' evaluation was no longer significant, but the continuous performance task was. So that's why I said before that -- that's why I had to make the decision to use the whole sample as the signal group for the evaluation.

DR. CASTELLANOS: Again, I haven't seen the data and you have, but I suspect that – because, as

we've heard, there's a fatigue effect. This is an excruciating test. It's very effective for picking up medication effects, because if you can do a CPT, then your medication is really working well. It's 15 minutes of paying attention to letters or whatever various versions of that.

So that's the kind of thing within subject comparisons, particularly salient, because if you're missing one of those data points because the kids just said, "I'm not going to do it this week," then you wind up losing that. So I suspect that that's partly why you have a greater power with the complete data set than you do with the others. But, again, I understand that there's always a tradeoff.

DR. SOBOTKA: Yes. If we go with that route, then, we'll have to say, well, the parents' evaluations were not significant. So it's still no confirmation of an effect, depending on which one of these analytical approaches you use.

DR. ACUFF: Dr. Burks?

DR. BURKS: To get back to the specific questions that we're being asked here, the first one

is, are the review criteria appropriate, and then the second one is, should we need additional criteria. And I think what I understand is, really, of the initial criteria, the only one that might be questioned is the last one and how much weight was put there. And I think what we're talking about gets to that issue for the FDA to consider. But I don't think that anybody is saying that the review criteria that are there, other than that, are not appropriate.

I think to move the discussion along, we're talking about the specifics of the study. That's not really pertinent to this question right now. It's pertinent to question number 2.

DR. ACUFF: Right. I agree.

So can we vote, or do we need further discussion?

[Brief discussion off microphone.]

DR. ACUFF: Now, we have these clickers, and you should have one on your nameplate. It should be behind your name. So you have the option of pressing 1 or 2, 1 for yes and 2 for no. And so this should record our votes and produce a bar chart

instantaneously. So we can go now.

[Voting.]

DR. ACUFF: So we have 93 percent yes; 7 percent no.

So let's go to the next question, which is 1B. So in the review of published research presented in overview and evaluation of proposed association between artificial food colors and attention deficit hyperactivity disorders and problem behaviors in children, the studies were evaluated based on criteria descried in part 3 of the review. Are additional criteria needed, yes or no?

So you can go ahead and vote now.

[Voting.]

DR. ACUFF: So do we have votes for everybody on that one? We did.

All right. So 57 percent yes; 43 percent no.

So let's go to the second question then.

DR. WINTER: Just a point of clarification. Is everybody on the committee allowed to vote or just the -- are the non-industry and non-consumer members allowed to vote?

MS. JELETIC: The industry reps do not vote. The consumer reps do.

DR. WINTER: Okay. Thank you.

DR. ACUFF: All right. Question 2. Do the current relevant data support FDA's conclusion as set forth in the September 1, 2010 interim toxicology review memorandum that a causal relationship between consumption of certified color additives in food and hyperactivity in children in the general population has not been established?

Discussion? Dr. Waldrop?

MR. WALDROP: A point of clarification. Are we also including the concept of other behavioral components in this?

DR. ACUFF: Yes. I think in terms of changing that in our charge, then it will be assumed through the remainder of the questions.

Dr. Burks?

DR. BURKS: To address this larger question, which, obviously, is a major reason that we all have come together from different disciplines, as a clinician seeing patients, I can't tell you how the

outcome of what we're going to talk about and vote on will be important for the public, individual patients and families.

Right now, this view of the food additives and its affect on hyperactivity and other learning is really kind of a sidebar of traditional medicine. Good or bad, that's where it's viewed for the reasons that we've looked at with all the different studies.

If we vote to say that it's not that, it doesn't change, it's not going to change the world, but at the seam time, it's going to send a major message to the medical community, the lay community, that we feel like there's a major thing there.

I think we just need to -- we're not going to be able to decide the nuances of each of the studies, but I think it is a pretty significant issue that we're going to send a message, a major message to the FDA, but, more importantly, to the scientific community, the medical community and the lay public that we've come from different disciplines and we really think that there is a major issue here, because that's not where it is right now.

To elaborate on that further, we've looked at a lot of different studies. There are lots of different results, and we could parse out all of them. I think some of the major studies we've looked at, that show some effect, there are issues there. The review that we looked at yesterday was done. I'm not being critical, but critical thinking was done by a medical student without content knowledge of either the subject or biostatistics, and we have to take that into account. Most of the studies we're talking about are in pretty low tier medical journals for reasons that were talked about, because of the lack of good quality study design. Again, it's not being critical, but just thinking with critical thinking about the studies that we're talking about. So it's important, I think, that we look at that.

We've heard lots of people, both there -- and their testimonials about the effect that it has on a family, and those are real, but there's also a 30 percent placebo effect in everything that we do in medicine. We understand that. And I think, again, we have to take that into account.

For most food-relate studies, at least immunologically, you can't just have an effect one time; that you introduce the food, you have an effect, you take it out, you reintroduce it to see if the same effect is there. So it's reproducible. None of these really do that scientifically. I think it speaks to the scientific quality of what we're talking about.

I'm not trying to get into the specifics of the study, but just the big body of work, that's where we are with it. And, again, I can't stress the importance of what we're going to talk about and vote on, because that's a major message that we're going to send to all the communities.

DR. ACUFF: Dr. Gray?

DR. GRAY: This charge question, to me, asks a very hard question when it asks for us to decide whether there is a causal relationship. It's very different, in fact, even than the legal standard that we heard about from the FDA when we started, that Lisa has brought us back to several times. Reasonable certainty of no harm is different than believing that there is a causal relationship. And so I think that

answering this question puts us in a very different place, and we need to consider that this is the charge question that's been given us.

To me, it's just a very different standard, in my mind, than is the standard even that the agency is going to have to address when they decide what to do with the advice that we give them.

DR. ACUFF: Dr. Jones?

DR. JONES: Tim Jones. I would just like to strongly reiterate Dr. Burks' comments. I think they're very important. And we've spent a hugely disproportionate amount of time talking about one study, the Southampton study, and good reasons for that. It's far and away the biggest and strongest, but everything is relative, and we have 32 other studies I think, as you've said, that it's important that we don't forget about.

I don't think any two of them shared the same methodology, and every single one of them has strong -- I don't think one of them mentioned statistical comparisons. I mean, there are just a lot of issues with -- we have to view it as a body and not

make a very important decision based on one study.

DR. ACUFF: Ms. Lefferts?

MS. LEFFERTS: As I've sat here over the last day and a half and heard everything, I feel like pieces have been coming together in my own mind. The understanding of and definition of ADHD has been evolving rapidly, and it's still evolving, and this has had an impact on the studies done over time. We're talking about something that is persistent across the life span. It's quite prevalent, has very serious consequences, and its causes are multifactorial.

As Dr. Castellanos said, the word "causes" is kind of tricky here. Also, the words "trigger" and "exacerbate" have been used. Like asthma, there are causes, there are triggers. They're different. And this is something we haven't had a lot of chance to discuss, unfortunately.

But the other thing, I guess, that struck me is that there is a spectrum of behaviors, which, at their extreme, can culminate in a diagnosis of ADHD, which have a normal distribution in the general population, and keeping in mind, again, that

understanding and measuring effects on behavior is really pretty tricky. It's not cut-and-dried. It's not like measuring blood pressure.

We have many available studies looking at how artificial color additives affect behavior done at doses lower than we would like and done with sample sizes that are much lower than we'd like. Nevertheless, rather remarkably, many studies have shown an adverse effect on behavior.

Are these spurious? I don't think they are. The Southampton study is the largest and most powerful study to date on the impact of artificial colors on behavior, and it looked at the general population and not those at the extreme end of the spectrum. And, again, yet it found an effect, an effect which replicated the results of an earlier study, which is very significant.

Now, while not all the mixes produced statistically significant results, it's important to note that the ones that didn't were just shy of significance. It's not like they showed no effect or that they showed the opposite effect.

So I think we have to be smart about this and not just say, "Well, they weren't all statistically significant, so it's not important." We're seeing that there's an increase, and when we keep that in mind with all these other limitations that were likely working against seeing an effect, it makes it all the more compelling, to me.

Another issue that's come up is, well, maybe it was the preservative used in both mixes that could have been responsible for the effects seen and not the dyes. Of course, that's possible, but it seems highly unlikely. We don't have any studies on this particular preservative linking it to behavioral effects, but we have a lot of studies linking dyes to behavioral effects. And we have a lot of testimony from consumers, some of them who have really tried to study this in their own ways very carefully. And, of course, the preservative is not the only component in common in mix A and mix B. So I don't know why we focused on that so much. Yellow 6 was in both mixes, for example.

So I guess I've already mentioned the criticism that we're not always seeing results in

multiple settings, it would have been nice, but I don't think, again, that it takes away from the fact that we're seeing something here with color additives. There's something going on. Parents know that. This is hard to measure, but I don't think -- you know, are we going to wait for another 50 studies to be done before we take any -- before we reach any conclusions?

I guess, I understand that there are scientific questions and then there are public health questions, and I would hate to see this committee leave without any recommendations with regard to the public health, and that was why I had hoped to change the charge somewhat.

But I feel very convinced that there is something going on here, and there are a lot of unknowns, but the picture is starting to fill out in a way that makes sense. And when I look, for example, at the Bradford Hill criteria, which I did last night, trying to go through things, there's a lot of reasons I think to weigh the evidence in favor of some kind of positive relationship; whether you call it causing, triggering, it sort of depends on the particular

endpoint you're measuring. But there's something going on here, and I would hate for us to just say, no, there's no causal relationship.

That's it.

DR. ACUFF: Dr. Blakistone?

DR. BLAKISTONE: When we began yesterday, we heard from Mr. Kraemer sound science, and certainly industry looks for sound science, repeatable results. We've discussed reasonable certainty of no harm in the general population, and I think that's where I personally get hung up, that we're not seeing repeatable results in the general population.

So I'm keen to hear the committee discuss this, because I know industry is really, before all stops are pulled, massive reformulation, massive labeling, perhaps changes, that we really would like to feel totally comfortable that the general population is going to benefit from this, and I don't have that sense right now.

DR. ACUFF: Dr. Voorhees?

DR. VOORHEES: I would like to go back to what Dr. Gray said. This question is set at a fairly high

bar, and I would say that because the data that we reviewed, the clinical, the human studies, they do all have serious issues. And it's often said in science, you can't build a bridge across the river with partial -- you can't reach the other side with partial sections. Right? No matter how many partial sections you put, unless you have enough sections to span to the other side, you can't draw the conclusion of cause and effect. And, to me, that suggests that the data do not meet that standard, that we can't -- I don't see how the data can be interpreted as a cause of behavioral disturbance or hyperactivity or contributing to hyperactivity. It's not at that level.

Whether it has any association or any contributing factor, that's another question, which I hear Ms. Lefferts speaking to, but in terms of the way that's phrased, as a cause, I don't see the data as rising to that level.

DR. ACUFF: Dr. Castellanos?

DR. CASTELLANOS: I agree. But this is the field that had its heyday in the late '70s, early '80s. There was a flurry of activity, a focus on food

additives, as well as even larger literature on sugar, which we've not even mentioned, which was conclusively negative. And those dietary wars, as they've been described to me by my mentors, were fought and conducted. And for the past couple of decades, for the most part, the standard position has been, we took care of this problem, there's nothing there, to the point where, as we've heard, the NIH makes explicit that they will not support any further inquiry in this area. The only reason that the Southampton studies occurred was because they were sponsored by a food agency at the U.K.

So we're left with a science that can't support a causal claim, the bridge span is not there, but it also doesn't support the absence of causal claims. In fact, it's mute or unintelligible. It's an embarrassment. And yet, the position that this statement represents will continue to impede the possibility of bringing science to bear.

That kind of science will have to take a different shape from what's been done. It's not going to happen that IRBs, the parents, the funders are going

to provide the kind of support and ability to conduct the complex kinds of studies that would be required to tease this out, the dose-response issues, the combination of medications, the multiple measures within subject designs. It's just not going to happen.

But whatever clues are going to be pursued, whether they have to be related to histamine or other kinds of genotypic variations and recruiting people on the basis of genotype and then looking at whether or not there are specific outcomes that can be pursued in those ways, those sorts of questions that perhaps should be pursued will be stillborn if we assume that the very extremely imperfect data that we've looked at is sufficient to say that we're comfortable with the lack of a causal link.

As I've mentioned, causality is a distant aspiration, but certainly these data don't give us any confidence that we can say there's nothing to worry about here, this problem is taken care of, this shouldn't be looked at.

DR. ACUFF: Mr. Waldrop?

MR. WALDROP: I'm going to agree with

Dr. Castellanos, and he said it much more eloquently than I probably will. But I also want to raise an issue with this terminology and the way that FDA has crafted this question. I think it does a disservice both to the issue and to those that are interested in it, where we could have maybe looked at several different variations of this and gotten a little bit further down the road and maybe started pointing directions -- know we're going to talk about other studies in a later question. We could have started pointing directions in terms of the issues that are important and the issues that we need to look at more thoroughly.

I think we are seeing some effect in some children. I think the Southampton study was, to my mind, showing an effect in the general population, and that is I think a relevant issue that certainly needs to be explored more, as others have said.

I'm also concerned that by shutting the door right now, that's going to cause some -- it's going to limit the ability to further explore this the way it maybe needs to be explored.

DR. ACUFF: Dr. Jones, then Dr. Voorhees.

DR. JONES: I think Dr. Castellanos said it very well, but I think we have to be really careful not to mix the answer to this question with that of question 5, which is are more studies needed. And I suspect it would be very hard to vote no to that question.

[Laughter.]

DR. JONES: But I don't think that we should use this question to emphasize or to make the point that we will make with question 5, which is do more studies.

DR. ACUFF: Dr. Voorhees?

DR. VOORHEES: I, too, agree with Dr. Castellanos, but I would maybe disagree at the last part, which is that this is going to really end this issue. It doesn't seem to me that it will. I mean, in medicine, there are many examples of issues that go on and on and on. Hormone replacement therapy went on endlessly until NIH mounted a huge number of studies at great expense. Hundreds of millions of dollars went into some of the final studies.

So I don't think the issue is going to go away. I think, in fact, the fact that it doesn't reach the level of causation may very well trigger additional studies to try to demonstrate whether it does or doesn't.

My hope out of this would be that it would actually trigger people to keep investigating this issue and trying to resolve it, trying to bring it to a better point of resolution, as often happens in medicine with various treatments.

DR. ACUFF: Dr. Castellanos?

DR. CASTELLANOS: I hope that that holds up, but I suspect that what happens in these situations is that thoughtful people come together for a couple of days, really grapple with these questions, and what emerges from these are very straightforward conclusions that then do have a great deal of impact.

The stance in the field that I work in is that this is a dead issue and that there's no reason to devote resources to it, and that's maintained by us as peer reviewers. The likelihood of a proposal making it through the study section process and not running

aground, at least one of the three reviewers is going to say, "Ah, we've done this, an FDA panel just looked at this, and they agreed with everyone else that there's nothing there." That's the way in which this particular question will be interpreted. And I find that absence of evidence is not evidence of absence. We don't have the data to support the assertion that there's no relationship. We really don't.

DR. ACUFF: Dr. Burks?

DR. BURKS: I appreciate that view, although if you'd turn it the other way around, do we really have evidence that there's something there?

DR. CASTELLANOS: We don't have it.

DR. BURKS: We don't have evidence that it's there, scientific evidence. You say that they don't reach statistical significance. That's why you do statistics, so that it's not there. There aren't good studies to show that it's there, that there is an effect there, and it's consistent over different studies. That's what you're looking for.

If you're looking for an absence of evidence, that's huge population studies. We're talking about to

look for evidence that really there is a signal there. We don't get that from the studies. I really don't think that we do.

I understand your point about like a study section and not being studied, but at the same time, a vote -- you say a yes vote would do that in a study section. My concern would be more from the public, what we're telling them, a mother with a child now looking at a label, what she's going to do. To me, that's a huge, bigger ramification. You have immediate results.

A study section, I like it to be studied, but that's a minor point, to me, compared to what you're going to tell a mother with a child about these things that she's not going to want to give her child if we say, yes, they're related.

DR. ACUFF: Dr. Castellanos?

DR. CASTELLANOS: I apologize for belaboring this, but you've mentioned statistical significance. This is a complex issue in and of itself. The use of statistical thresholds is meant to give us some guidance as to the likelihood that results are

spurious. What's been mentioned, but not emphasized, is that much more relevant is the issue of prior probabilities and confirmation.

Dr. Stevenson mentioned that the Isle of Wight study detected a signal in parent ratings, as that may be the case, which then was designed -- the Southampton study was designed, in part, although it's been criticized, to, as precisely as possible, replicate that effect. What we've heard is that the parent ratings largely drove a confirmation of that result.

Statistically, the finding of an association and reconfirmation in an independent data set vastly increases the likelihood that there is a real association there, beyond the typical p-value that you get from a single study. What we usually deal with is initial results, which we all know are inflated. But the combination of two independent data sets that basically converge does significantly enhance my confidence that there may well be something there.

The problem with the Southampton study, as we've all heard and reiterated, is that for, again, many good, well intentioned reasons, it included sodium

benzoate, which may or may not be a player. So it keeps us from making definitive assertions about the specific tight question of food additives. But the statistical significance issues we've only glancingly mentioned, and that issue of two separate independent studies, in my field, that's big stuff.

DR. ACUFF: Dr. Jones?

DR. JONES: Yes. But we also have 32 studies where they did everything possible to make the pretest probability as high as it can be, and far higher than in the general population.

DR. CASTELLANOS: Most of those -- I mean, it's really a humbling process to read where this field has come from, but with samples that are so grossly inadequate, even the Southampton study is really poorly powered, but was the extent of how much the funding was going to achieve. That's a very large study by comparison to the others, but you have a whole literature full of inadequately sampled studies. With all of their other design flaws, I really don't think -- again, those are mute data.

DR. ACUFF: Further discussion? Ms. Menke-

Schaenzer?

MS. MENKE-SCHAENZER: I just wanted to reflect a moment around our charge to be science-based as a committee. And I'm hearing things like the studies are very extremely imperfect data, "There's lack of causal link. We haven't reached the level of causation." And I just want to remind us of our mandate to be science-based. And this question is specific to is there a causal relationship between consumption of certified colors and additives.

Like was brought forth before, I don't want us to get question 5 -- I think everyone in this room absolutely would agree that there is more research needed mixed up with this question, and I'd just ask us think about this specific question at hand and the science and the imperfect data that we've reviewed.

DR. ACUFF: Again, the question is do the relevant data support that a causal relationship exists. And the question that we're actually asked to define you need to be careful with, because it's worded in such a way that you might vote yes when you meant no. So let's read it carefully.

Do the current relevant data support FDA's conclusion, as set forth in the September 1, 2010 Interim Toxicology Review Memorandum, that a causal relationship between consumption of certified color additives in food and hyperactivity in children in the general population has not been established?

So if you vote yes, you vote that their document is correct that it has not been established; no, that their document is wrong.

[Voting.]

DR. ACUFF: Has everyone voted? We're going to do it again.

[Voting.]

DR. ACUFF: Okay; 79 percent yes; 21 percent no.

Let's move on to question 3. The National Institutes of Health's 1982 consensus development panel on defined diets in childhood hyperactivity concluded that for some children with both ADHD and a confirmed food allergy, dietary modification has produced some improvement in behaviors.

The panel recommended that elimination diets

should not be used universally to treat childhood hyperactivity with or without the presence of food allergies since there is no scientific evidence to predict which children may benefit. The panel, however, also recognized that initiation of a trial of dietary treatment or continuation of a diet in patients whose families and physicians receive benefits may be warranted.

Are these conclusions and recommendations still relevant today in light of subsequently published studies, especially as those conclusions and recommendations apply to certified color additives?

Discussion? Dr. Burks?

DR. BURKS: I guess a couple things. One, I don't know that we really talked or had enough information about the consensus development panel in detail, other than just looking at it as one of the other documents that we had a cursory look at. So I think this question of the five or six that we're doing I think is more problematic.

The second thing is, while some of us might disagree with the conclusion, it may be on the basis

that we feel like there is a lot there and it should be done in more kids. Others might disagree with the statement, meaning it shouldn't be done at all. So a note vote doesn't mean the same thing.

So that's why I think it's problematic, one, that we're addressing it, because it really isn't kind of what we were talking about mostly, and, two, it's going to be an ambiguous outcome.

DR. ACUFF: Dr. Gray?

DR. GRAY: I'd like to agree with Dr. Burks actually on both counts. To start with the second one, I think we need to get an English major in to help with the question to make sure that we didn't end up in an ambiguous position.

The second is that I personally don't feel comfortable that we have delved into the entire issue of dietary modification sufficiently. We have been focusing primarily on a small part of that with the artificial food colors. And, for example, I don't know that the literature that we see here is a complete look at the literature on dietary modification, because from my read of this, it was focused on looking at studies

that had a specific emphasis on food colors.

So I think like Dr. Burks, I'm a little uncomfortable with this question.

DR. ACUFF: Dr. Vugia?

DR. VUGIA: Thank you. I agree somewhat. I also want to clarify that maybe the wording could be changed, because I think what the question is trying to get at is given what we were presented with, looking at the concern about food colors in diet for some parents, we didn't delve into the issue about diet elimination and how effective that is. But we were given a review of those studies that include food colors. And in light of those studies, would the panel recognize that parents and physicians may continue this if they feel it's needed.

I think some rewording of the language is probably needed here, and I agree that the language here is such that we did not -- it assumed that we actually have looked at the total picture; in fact, we weren't given a chance to do so. So the last sentence there probably should be reworded or some wording should be changed so that it would be more specific as

to what the panel should be voting on.

DR. GRAY: I'd be much more comfortable with discussing it in the way that Dr. Vugia has just described.

DR. ACUFF: Dr. Voorhees?

DR. VOORHEES: I'm comfortable with that language. It seems, if I can put it this way, rather benign. If parents and their providers wish to try some kind of special diet, why wouldn't we say that it's still a reasonable thing to try? We can't say that it's not reasonable. We don't have enough evidence to say it isn't.

DR. ACUFF: Dr. Burks?

DR. BURKS: This really is addressing -- if you look at our question, it's addressing kids that have ADHD and confirmed food allergy. We have not had any discussions about food allergy at all. We've talked about food additives and their relationship to behavior in a specific population and the overall population. We have not talked about ADHD in kids with food allergy. It's really a different issue.

At the time the consensus document was done,

then that was a minor part of what came out of that. The biggest part was like there's not a relationship with food additives; that there may be a small set of that group and there may be something there, but that's not what we've been talking about. We've been talking about food additives and behavior, not food allergy and ADHD. So it's a really different question.

DR. ACUFF: Dr. Jones?

DR. JONES: And I agree. I'm comfortable answering the question for the reasons that you said. And this is a treatment question. It's got "treatment" in there twice and the word "color" is not in here. So we can give our opinions, but I don't think we talked about it much.

DR. VOORHEES: Also, it says, as far as the point that Dr. Burks is making, it says, "with or without the presence of food allergy." So that clause kind of throws that part out, in effect. By saying with or without, it's like whatever.

DR. ACUFF: Ms. Lefferts?

MS. LEFFERTS: I agree that we have not talked about treatment. I also find the word "relevant" very

problematic.

Are recommendations issued almost 30 years ago relevant today? Well, they're relevant. Do we necessarily completely agree with them? That's a different question. Recommendations, science is always evolving and building, and so everything is relevant, but clearly a lot has happened in the nearly 30 years since those recommendations were established.

So I'm concerned if we're sending a signal that we kind of think nothing has changed since then. There's been a lot more study, in general, on the issue that we've been talking about, which is not treatment.

DR. ACUFF: I'm going to ask Dr. Cheeseman to clarify their intent in the question, make sure that we know for sure what they wanted, and if we can alter it or if we need to deal with our issues.

MR. CHEESEMAN: I'm sorry. I've had a little bit of a family emergency which is ongoing. But if you could refresh me with the question.

DR. ACUFF: We're dealing with question 3.

DR. CHEESEMAN: Yes.

DR. ACUFF: Dr. Vugia, why don't

you -- because I think you tied it up nicely.

DR. VUGIA: Yes. Several committee members have raised the issue that question 3 is not entirely clear in the sense that it talks about the NIH consensus development panel recommendation that actually focused on looking at ADHD and confirmed food allergy and dietary modification regarding that issue.

We did not delve into that particular issue in detail. What we have dealt with in the last couple of days has been particularly focused on color additives. And, therefore, when it comes down to the last part of the question or the last sentence, "Are these conclusions and recommendations still relevant today," in light of subsequent studies that we were discussing, as applied -- especially as these conclusions and recommendations applied to certified color additives.

We wonder if the wording can be changed to clarify, to make clear that we're only talking about color additives toward whether parents and providers could still recommend a dietary consideration of these additives.

DR. CHEESEMAN: I heard most of that

discussion and would -- I don't see an objection to -- I think it's a legitimate criticism with regard to the amount of information that we were able to give you and the time that we had to discuss on this particular issue. So I don't think we should have an objection to that type of a change.

DR. ACUFF: Are we understanding the purpose of your question? Are we getting it, I guess?

DR. CHEESEMAN: This question is aimed at trying to -- we're really trying to build on the consensus that came out of the NIH panel in 1982 to ensure that we are doing what we need to do with regard to public health recommendations as far as what options families and their physicians should pursue. So I think so.

DR. ACUFF: So the question is -- the panel recommended that these diets should not be used universally to treat hyperactivity. But if families and physicians perceive that there are benefits, we're certainly not saying that shouldn't be done.

Is that the crux of your question?

DR. CHEESEMAN: Absolutely.

DR. VOORHEES: Is the key sentence, "The panel, however, also recognized that the initiation of a trial, dietary treatment, or continuation of a diet in patients whose families and physicians perceive benefits may be warranted," isn't that the key part or can we just keep that part?

DR. ACUFF: Yes. That's the key part.

DR. BURKS: But the diet, we're talking about just food additives. We're not talking about foods in general.

DR. CHEESEMAN: Right.

DR. BURKS: That's all we've been talking about.

DR. CHEESEMAN: Right. I would agree with that.

DR. ACUFF: Further discussion?

Thank you, Mitch.

Any additional discussion?

MS. LEFFERTS: Could you just clarify? I'm a little confused. You can pick sentences out of here that you like, and you can pick sentences out of here you don't like, and we can pick sentences out of here

that we really have no business really voting on, because we didn't discuss them. So I'm a little bit unclear as to exactly what we're being asked to vote on.

DR. ACUFF: Okay. I will try to clarify it, as I understand it, and then you guys can tell me where I missed.

My understanding is that the National Institutes or the NIH panel recommended that elimination diets should not be used across the board universally to treat childhood hyperactivity because there was not enough scientific evidence to support a universal recommendation on that. But they recognized that in certain families where physicians perceive that there are some benefits, that those are certainly warranted, and they didn't want to discourage that situation.

Did I get that right? Dr. Gray?

DR. GRAY: So in light of the evidence that we have looked at that, that has come since 1982, do we agree that that is still appropriate advice in the case of color additives?

DR. ACUFF: Exactly, yes. Has anything happened since then that has changed that recommendation? Do we still agree with that recommendation or would we say no?

Dr. Burks?

DR. BURKS: The one other part that's pertinent, the NII, they just released their food allergy guidelines in December that have a section that has some of this to be addressed in it. And so that's why I'm saying, from a food picture standpoint, then those guidelines say there's no relationship.

So if we're just talking about food additives, to clarify that and make sure that's what we're going to vote on, but even those guideline wouldn't be this strong. They wouldn't say it's okay to go ahead and do it if you want to. That's not where they're going to come from.

DR. ACUFF: Dr. Freeland-Graves?

DR. FREELAND-GRAVES: I don't think that's a very strong recommendation. I think it's kind of very mild. So I don't see any reason why we shouldn't vote on this yes.

DR. ACUFF: Ms. Lefferts?

MS. LEFFERTS: I guess my reluctance is that I'm concerned that by -- you know, who's to say that if someone feels that a diet could help them, that they shouldn't do it? But it sort of sends a signal to me that we're kind of saying nothing has really changed in the last 30 years to change our view on recommendations made then, where, in fact, we have had the Isle of Wight study, we've had the confirming Southampton study. There has been a lot that's happened since then.

I don't know how to -- I'm personally at a -- it's going to be very difficult for me to vote for this because of these two -- because of the conflicting signal I'm concerned that we'll be sending.

DR. ACUFF: Well, I think the key for me in this is the statement, "The panel recommended that elimination diets should not be used universally to treat childhood hyperactivity, since there's no scientific evidence to predict which children may benefit." So I think the universal approach in terms of application is the key to this, unless I missed the

point.

MS. LEFFERTS: Yes. But if you're a parent, certainly, a dietary approach is a lot -- there are concerns with a medication approach, and a lot of parents would certainly rather take a less -- I'm losing my words -- a less intrusive treatment approach. And why shouldn't they try something less intrusive, less invasive first that's milder? It just kind of makes sense to me, if I were a parent, that that's what I would want to do.

DR. ACUFF: And I don't think I'm disagreeing with you, because I think that's the second part of the statement, that they recommended that initiation of a trial of dietary treatment or continuation of a diet in patients whose families and physicians perceive benefits may be warranted. I think the statement is this shouldn't just be universally applied, but if families and physicians feel like there's a benefit, certainly; certainly do that.

Any other discussion further? Are we not saying the same thing, do you think? I think I'm agreeing with you actually. Maybe not.

MS. LEFFERTS: I'm not really quite comfortable with this whole question. I still am not comfortable with it, but I may be the only one that feels this way. But, to me, there's no scientific evidence to predict which children may benefit is a pretty harsh statement. I think there is evidence that a dietary approach could be beneficial. We've seen that in studies. We've heard that from parents, how much this has helped them, and it's sort of really downgrading the importance of this approach and sort of saying, "Well, if you want to do it, okay."

I just think that doesn't really do justice to the evidence that's accumulated in the last 30 years since this recommendation was made.

DR. ACUFF: Okay. Well, I understand your comment, and I think I am looking at it from maybe the glass is half full, and I'm looking at it half empty maybe.

Dr. Castellanos, go ahead.

DR. CASTELLANOS: Well, even an aggressive reading of the Southampton studies wouldn't lead to a recommendation that elimination diets be instituted

universally. That seems so far beyond the relatively weak evidence that exists.

I think that the way that the question is phrased, it's almost impossible to say how we could vote otherwise than yes.

DR. ACUFF: Okay. So we're ready for a vote. All right.

So the panel, however, also recognized that initiation of a trial of dietary treatment or continuation of a diet in patients whose families and physicians perceive benefits may be warranted.

This is the second part, right?

Are these conclusions and recommendations still relevant today in light of subsequently published studies, especially as those conclusions and recommendations apply to certified color additives? Yes or no?

[Voting.]

DR. ACUFF: Yes is 93 percent; no is 7.

Do you want a break or keep going? Okay.

Question 4. Under current FDA regulations, the label of any food to which a certified color

additive has been added must declare the color additive as an ingredient by its certified name; for example, FD&C Yellow Number 5.

In light of the scientific evidence presented to the committee concerning the consumption of certified color additives in food and hyperactivity in children, what additional information, if any, should be disclosed on the product label of foods containing certified color additives to ensure their safe use in food?

Discussion? Ms. Lefferts?

MS. LEFFERTS: Well, we heard a lot about material, what's relevant, what's material, in a legal sense. And there's no doubt that color additives can cause adverse behavioral effects in some children. We've seen that in certain studies. And I think that this is important information to give on the label.

We've heard from many parents who, of course, would assume that the food that they're giving their children and the additives that have been approved by the FDA, of course, it must be safe. It doesn't even occur to them that there could be any link between

these color additives and the very serious behavioral problems that some of them observe in their children.

So I think this is certainly material to the consumer, and that it would be advisable that the label should contain a warning statement such as the one that had been proposed by the petitioner, which said, "The artificial colorings in this food cause hyperactivity and behavioral problems in some children." It could just say, "The artificial colorings cause behavioral problems in some children." I don't think that's controversial that they do cause problems in some children.

DR. ACUFF: Dr. Voorhees?

DR. VOORHEES: I took a somewhat different approach toward the idea of a label, and whether you like it or not is something you can all discuss.

I would go with more of an approach of FD&C color additive, whatever it is, the number, has not been adequately tested for safety to brain development and behavior during pregnancy, infancy, childhood or adolescence.

DR. ACUFF: Dr. Blakistone?

DR. BLAKISTONE: I think that gets at more information to just say -- put a warning label on there and say that that particular dye produces or may produce an effect in some children really doesn't give you much of a base. But if there had to be a warning label at all, which I think sets a very bad precedent for FDA, I kind of like your alternative approach.

DR. ACUFF: Dr. Jones?

DR. JONES: A couple things. I think that Dr. Burks' comment on the last question applies very well here in terms of societal implications, but some of this, I guess, has to do with threshold and how serious and pervasive something has to be in order to justify a label.

But if we put a label that long or a statement that long on every chemical and ingredient that hasn't been adequately studied in newborns and fetuses, or could cause allergic reactions that are dangerous, especially when we use words like "may" and "suggestive," I mean, you wouldn't see the package anymore. So it's a question of relative concern or severity, and that's a hard one.

DR. ACUFF: Dr. Burks?

DR. BURKS: A few years ago, the Congress passed the Food Allergy Labeling Act that the FDA helps enforce to label the eight major food allergens, which was good, because prior to that time, the families -- if it had milk in it, it said sodium caseinate or potassium caseinate, and they didn't really understand that.

Well, the outcome of that has been actually worse for the public than that labeling, because there are so many "may contain" labels. It says "may contain" because it's manufactured on the same line, manufactured in the same plant, manufactured in the same county, whatever it may say. And it's harder for a family now that has food allergy to decide what food to eat because of that "may contain" labeling.

For most people -- and they've done studies, the FDA has done studies -- there's maybe a 5 to 10 percent contamination rate in that "may contain," but that means all those families that have kids that are allergic to one of those foods, if it says "may contain," they're also avoiding all those others.

The "may contain" far outweighs those that actually have the allergen there. So it really has huge implications. It's harder for a family to eat now, to go to the grocery store with a child who is peanut allergic than it was 5 years ago because of the "may contain" labeling.

DR. ACUFF: Ms. Blakistone?

DR. BLAKISTONE: I was just thinking about California Proposition 65, and my understanding of it is that there's so many compounds now that have fallen under that legislation that Californians are pretty much desensitized to any consideration or any benefit that that kind of labeling brings. And I think that's kind of precipice that we're on if we do consider advising a warning label.

DR. ACUFF: Mr. Waldrop?

MR. WALDROP: I think this gets us back to that issue of convincing evidence of no harm, and I think the scientific evidence that's been presented to the committee has cracked that and has demonstrated that there is not convincing evidence of no harm, that there are some effects for some children.

So if parents want to know -- parents aren't going to be able to -- parents who are really interested in this will know all the food dyes and be able to go and identify them when they read the label. Not all parents who are concerned about their child's behavior may have heard about a link between food dyes or other elements, may know all that information.

So this would give them a little bit of information that they can then say, "If I'm trying to address this problem with my child, some substance in this food may affect my child." So I think a warning label in that sense would be useful.

Just speaking for consumers generally, they do want more information about their food, they want to know what's in it, and this would be additional information that would help them.

DR. ACUFF: Ms. Blakistone?

DR. BLAKISTONE: I think there are so many caveats to this issue that there has to be another mechanism that FDA uses to convey the information to really help a consumer fully understand what's going on here, and that can't all happen on a package.

DR. ACUFF: Ms. Lefferts?

MS. LEFFERTS: I was just thinking about the comment about Proposition 65, and my understanding is that Proposition 65 led many companies to reformulate their products so that they could avoid putting a warning label on. I suspect that that would happen in this kind of a case. It can happen. We know it's happening in Europe.

So there's no reason why that can't happen, and there's certainly no reason why there can't be other sources of information made available by the FDA to consumers who would like more information, on the website or education materials, et cetera. But still, the label is kind of where the rubber meets the road, and this information is important to consumers and it does -- anyway, I've said -- it would reach a lot of consumers who otherwise would not know that there could be a link between their child's behavior and the food that they're eating. I think this is material.

DR. ACUFF: Other comments? Dr. Castellanos?

DR. CASTELLANOS: I like Dr. Voorhees' suggestion, but it doesn't have brevity to it. And,

again, weighing the very imperfect evidence that's been put before us, the European Parliament's position to begin this process by alerting consumers that those particular dyes that were studied in the Southampton study may have effects on activity and attention in children seems a reasonable step.

DR. ACUFF: Dr. Gray?

DR. GRAY: I have to say that I'm feeling a little bit of cognitive dissonance, given the discussion that we had around question 2 and the fact that we felt, as a group, not completely -- the discussion we had around the causal relationship, is there something here that suggests a causal relationship.

It leads me -- to me, that was kind of a scientific discussion that a group of scientific advisors are the right people to ask. To me, this is sort of a question that's going beyond that, and, in fact, the discussion of the European situation is a very good one. That was one where the scientists, the European Food Safety Authority, looked at the evidence and essentially came to the same conclusion that we

did; may be something, but it's not a very strong signal. And then it was the policymakers and politicians in the European Parliament who took the decision to label, and in fact they did it fully knowing that the scientists said there probably isn't something here.

That's why, to me, I'm a little uncomfortable that we're the right group to be thinking about whether we should be labeling something. I can imagine a lot of other kinds of other public health interventions I might want to take around this, and I'd want to evaluate them and look at their efficacy and try and understand which ones might work best, and that's a whole different kind of evidence and information that I want to consider.

So I'm not sure that we're the right group to actually decide whether labels are the best way or something else is the best way to deal with this.

DR. ACUFF: Dr. Blakistone?

DR. BLAKISTONE: When FDA puts a warning label on a package, particularly -- of course, I'm referring to this instance, to me, that means that this group has

decided there is a problem and a warning is needed to the population. And "may" words -- I have to go back to Dr. Burks' comment. I don't think consumers look at "may" words and pursue that to see whether their child is affected. They take it as serious.

DR. ACUFF: Dr. Jones?

DR. JONES: Tim Jones. I guess I'm sort of feeling like the last couple of comments, that if we start down this path, I feel like after looking at yesterday's evidence, we would almost be morally obligated to have this same conversation and put the label on about sodium benzoate, as a start, and maybe many other things, and I'm not sure where or if we could stop.

DR. ACUFF: Ms. Lefferts?

MS. LEFFERTS: Well, we don't have 50 double-blind studies on sodium benzoate. We don't have any linking sodium benzoate, just sodium benzoate, except for its inclusion in the Southampton study. So I don't think there's any comparison there.

In terms of the -- we've been asked to make scientific recommendations, and, also, FDA is a public

health regulatory agency, above all. When you go to its website, it says "what we do," the first word is in there is about protecting public health. So I think it's perfectly appropriate for our advisory committee to think about both the science and the public health.

I think the label -- I don't know of a better way to alert the public. I'm not suggesting that we use the word "may." If you may recall, the wording was that the artificial colors in this food cause behavioral problems in some children. There's no doubt about that. We know that they cause behavioral problems in some children, and that information is an important public health message to get out to parents who need this information.

DR. ACUFF: Dr. Freeland-Graves?

DR. FREELAND-GRAVES: I'm not sure that I'm comfortable lumping all color additives together and having a warning for all. The only one that would make me uncomfortable really would be the Blue Number 1, which crossed the blood-brain barrier. That would be my concern as a grandmother. But I just don't see lumping everything into one thing. So I respectfully

disagree with Dr. Voorhees.

DR. ACUFF: Mr. Waldrop?

MR. WALDROP: I think the next question we're going to get to in terms of future studies is going to be the easy one. I think all of us can agree let's study this, let's study that, let's throw all this into the pot and tell FDA to go out and find some way to get all these studies done.

That's going to take a long time, and until we get to that point, I think we are starting to see evidence that this is a concern for some children and a warning label can help -- can be out there in front helping the public understand that this could be a problem.

Then, later -- the FDA told us that they've removed warning labels after a time when they discovered there was a reason to do so. If, after we do all these great studies, and we find out that all these additives are completely safe, then the warning label could be removed. But I think right now, there's enough uncertainty and enough sort of direction pointing that this could be a concern that a warning

label is relevant.

DR. ACUFF: Dr. Burks?

DR. BURKS: I think what Tim said a minute ago about what's the level of concern before you label, I'm not sure that we're the right group to try to make that judgment. For some in the panel, that level is there. For others, it's not necessarily, but I don't know really, on 14 people, how we're going to really make an adequate judgment, because we don't really know what the criteria are to say, yes, we ought to label.

The second issue is related to the specific wording, like the one that you said earlier, when you say "some children," that's not how a mother or father reads it. They read it "my child," like they read "may contain," "it contains."

So to say it happens in some children, they have not seen this scientific literature to know if their child is one of those some or not one of those some. They read it as "my child." So basically, you're going to tell them that's a cause of it by labeling it like that, because they're not going to take into account that "some."

DR. ACUFF: Dr. Voorhees?

DR. VOORHEES: Well, I guess my feeling about a warning label is when you talk about causation, you're at a standard that's way up here, and then when you talk about a level of suspicion because there are some data that don't go away in these data -- I mean, they're not conclusive, but there seems to be some signal in there, and it just won't -- after 35 years, it won't quite go away. So I think it's within the FDA's latitude to simply express to consumers that there may be a concern.

Okay. So I don't know how consumers necessarily take the word "may," but I don't think that's -- I don't see that as my concern to determine whether people do or do not understand the English language. But you have to use the English language to convey the level of concern that exists. And if that's down here somewhere, so you would try to express it some way that's down here, there may be susceptible children.

DR. ACUFF: Ms. Blakistone?

DR. BLAKISTONE: I think we've hit on a major

problem, and I see it in the industry I serve, the seafood industry, with the FDA/EPA advisory on mercury in seafood. If you read through it, it's very well explained. People read that, and the conclusion they reach is, "Oh, that must be for me." Well, it isn't. It's a very limited population. So that's why I expressed my concern about a warning label. I believe that consumers read that and they take it as "I shouldn't be consuming this because it has such and such in it."

DR. ACUFF: Dr. Freeland-Graves?

DR. FREELAND-GRAVES: Can someone at the FDA tell us what the criteria are for a warning label?

DR. ACUFF: Jessica O'Connell?

MS. O'CONNELL: Like I said yesterday, FDA only has the authority to require a warning label about information that would prevent a product from being misleading, and one way a product can be misleading or a label can be misleading is if it fails to reveal information about the consequences that may result from the use of the product; so for food, consequences that may result from consumption of the food.

Material, again, is not defined, and it's a case-by-case determination, depending on a number of things. If the consequence is very serious, it might not have to be as pervasive. If it's more minor, it might have to be more pervasive, and that's done on a case-by-case basis. But it's consequences which may result from the use.

DR. ACUFF: Dr. Winter?

DR. WINTER: I just want to follow-up. You gave some examples yesterday of protein products used in low calorie diets, food containing psyllium husk and unpasteurized juice.

Can you provide any indication of the origin of what transpired to get FDA involved in making those label recommendations?

MS. O'CONNELL: I can speak specifically to the psyllium husk recommendation, just because that came from a health claim that was approved by FDA regarding foods containing psyllium husk.

So when FDA approved that health -- health claims have to be approved by FDA for use on food. When FDA approved that health claim through rulemaking,

the agency was concerned about the risks associated with consuming psyllium husk products, I think really swallowing issues if people didn't consume them with enough liquid. So it didn't want to approve a health claim that could encourage consumption of that product while there was this underlying risk that wasn't expressed. It's a balancing, again. If FDA is telling people to consume more of this product, they want to make sure that people are doing it safely.

So that particular warning statement came from that rulemaking. I don't know specific details about all of the others. I know the olestra, the same way. I talked about FDA doesn't require it anymore, but when it first required it, it came when olestra was approved, I believe. And then after further evaluation, FDA determined that it was no longer required.

It could require a warning statement based on its own decisions, based on a petition, and its response to a petition, based on any number of actions. It's just if FDA determines it's necessary to prevent that label from being misleading.

DR. VOORHEES: Could I ask? What was the original warning on olestra? What did it say?

MS. O'CONNELL: I don't have that. Does anyone know?

DR. ACUFF: Mitch?

DR. CHEESEMAN: I can only speak generally from memory, but it had to do with the testing data that demonstrated that olestra might scalp certain vitamins or reduce their absorption. And it also included, I believe, the information with regard to the fact that products with olestra were supplemented generally with those vitamins.

DR. VOORHEES: Did it contain the word "may"?

MS. O'CONNELL: I think it was "may have laxative effects."

DR. CHEESEMAN: I think you may be speaking to another product. There is a warning label on certain sugar alcohols to warn that they may have a laxative effect. So we've used the word.

DR. VOORHEES: You have used the word "may" in advice before.

DR. CHEESEMAN: Certainly, we've used the word

before. But, again, I would emphasize what Ms. O'Connell said about a case-by-case basis. There are more facts than the presence of that word with regard to that particular situation.

MS. O'CONNELL: I'll just offer that there are warning statements that use the word "may." The language of the statute uses the word "may." But, again, it really comes down to whether that information is necessary to prevent consumers from being misled. And so that's where the material issue comes in.

DR. ACUFF: Dr. Blakistone?

DR. BLAKISTONE: I wanted to ask Ms. O'Connell a general question. If FDA were to allow a warning label, things happen such that you were going to do that, would you be able to do that categorically for the dyes or would you have to look at evidence dye-by-dye, and sodium benzoate, too? But I'm particularly interested in the dyes.

MS. O'CONNELL: I can't answer that from a scientific standpoint, because I'm not a scientist. It would be whether -- if there were evidence to demonstrate that categorically color

additives -- there's material information about the consumption of color additives that FDA felt was necessary that consumers knew, then it could be done categorically. If it were information about a specific ingredient, then it could be done for a specific ingredient. But it really comes down to the evidence that FDA has and whether FDA determines that that is material in whatever context it is.

You can probably speak more about the scientific aspect of that.

DR. CHEESEMAN: I don't know that I could say more than the fact that it would have to be evidence-based.

One of the audience members has passed forward something off the Web on the olestra label. The label that I have says, "This product contains olestra. Olestra may cause abdominal cramping and loose stools. Olestra inhibits the absorption of some vitamins and other nutrients. Vitamins A, D, E and K have been added."

DR. VOORHEES: But not concise.

[Laughter.]

DR. ACUFF: Dr. Blakistone, did we already get yours?

DR. BLAKISTONE: Yes.

DR. ACUFF: Ms. Lefferts?

MS. LEFFERTS: I appreciate that answer from FDA, consequences may result. And we're talking about potentially very serious consequences, as we've heard. So particularly when you're talking about a product that's marketed to children, like brightly colored cereal that's obviously marketed for children, of course a consumer is going to assume that this is okay for children, and they have no idea, perhaps, if they haven't been reading up on these things, that there could be -- that a consequence may result to their child from consuming this cereal. It may not, but it may if their child is sensitive to the dye. So this is important for the consumer to know.

DR. ACUFF: Dr. Jones?

DR. JONES: Back up.

DR. ACUFF: This is for Ms. O'Connell?

DR. JONES: Yes. Tim Jones. So I guess I'm still trying to put this into context. But peanut

allergies, I mean, peanuts can kill people, do kill people, and it's not an uncommon allergy.

So why do peanut-containing products only having a label saying it's in there rather than a box saying what it can do to you?

MS. O'CONNELL: Well, like someone mentioned earlier, the allergen statements for the eight major allergens were directed by Congress. And so when Congress tells FDA to require something, FDA requires it. That was through FALCPA, which was an act passed by Congress.

So under that act, it has to have that "contains" statement if it contains one of the eight major food allergens. And so because we are directed to do that, we can promulgate regulations to enforce that, but that's the statement that was directed by Congress for those allergens.

DR. JONES: But you could certainly add more than that. They don't preclude adding another box.

MS. O'CONNELL: We could if we determined that more information was material. I can't speak specifically to peanuts, for example, because I'm not

aware of what discussions have been had within the agency regarding peanuts. But in a very general context, I can say that with regard to olestra, for example, FDA determined, when it stopped requiring the warning statement -- and someone can correct me if I'm wrong -- that the information about the possible effects -- while the possible effects were relatively insignificant, information about those effects was also very widely known.

So it wasn't necessary to require the statement any longer, because enough of the population knew about that, those effects. And so you could speculate that for something where the effects are widely known, it might not be necessary to require that information to prevent a product from being misleading.

Again, it all has to come back to what information would prevent that product from being misbranded, prevent the labeling from being misleading. So it's not just whether there are consequences that may result from the use, but whether those consequences are material and whether requiring that statement is necessary.

It's not allowing the statement. It's requiring the statement. So it's mandating that it appear on everything. So it's really more than just whether there are consequences, but about whether people have to know about those consequences.

DR. ACUFF: Dr. Fernandez?

DR. FERNANDEZ: I guess I'm still confused about -- is that a blanket recommendation? Because I know, for example, that in the Southampton study, they used just a certain type of food color, and the two of those that they used, they are prohibited in the United States.

So if we're going to say that a label should be added to the foods, are we going to differentiate between the different colors? I'm bringing this question to everyone, because we heard that Blue Number 1 has never been tested. And I agree here with Dr. Freeland that it crosses the brain barrier. And so what are we going to do about those that have not been tested versus the ones that have been exhaustively tested? How are we going to differentiate?

So it's very hard to use a blanket

recommendation when we don't have a specific effect of all the food additives.

DR. ACUFF: Mr. Waldrop?

MR. WALDROP: Just on the allergy issue, if somebody who is allergic to peanuts eats a peanut, they have a very acute reaction that's -- it's very quick to recognize. They have hives or they can't breathe or something like that. And so if you can see peanuts on the label and parents can read that, then they know not to buy that product. But with the food dyes, it's a little bit different, because the reaction isn't as acute.

DR. ACUFF: Dr. Voorhees?

DR. VOORHEES: I agree, and it is a concern that we can't differentiate the different food colors from the data that we've been presented, but that's the dilemma of the data we have. People study them lumped together, and so it's impossible for us to make a differentiation.

But I would say that if there's a chance that these materials produce an adverse effect on behavior, that's actually a more serious consequence than what

olestra does, and olestra rose to the level of a warning initially.

So I don't see why, if we think there's a possibility that some children have a more serious adverse effect than what olestra does, why we wouldn't want to warn consumers about that.

DR. ACUFF: Further discussion? Dr. Fernandez?

DR. FERNANDEZ: But, again, not all of these have been tested. So how can you differentiate? When you are going to make a claim like something may happen, you have to be very sure about that. And some of those have never even been tested in any study.

So you are going to lump them all together? That's my question.

DR. ACUFF: Further comment? Ms. Lefferts?

MS. LEFFERTS: One way around the concern that was just raised is to simply state "mixtures of artificial colors." That's what has been tested, and, of course, consumers are exposed to mixtures. So while on the one hand, it would be great to have chemical-by-chemical studies, it also is valuable to have mixtures,

because this is more what represents the real world.

I guess I'd like to just think for a moment, if we decide not to have labels, then what? If we decide not to have labels, then we're saying that we're knowing that a lot of consumers out there are not going to be aware of this information, which could be very important to their child.

There's been a concern expressed that maybe we're alarming consumers and that they'll think it's definitely their child. I guess I have a little more faith in consumers than that. And if we don't give them this information, then we know that there are going to be parents struggling, families are going to be put under tremendous stress.

We know this. In fact, it's been happening -- we've heard today during the public hearing portion of the meeting, there was a woman who was a physician, highly educated consumers, intelligent consumers that were struggling to uncover this information. And there are probably many consumers that haven't uncovered that information, and we know there will be more consumers that won't know about this

unless we put the information on the label so that they can learn it.

DR. ACUFF: Dr. Burks?

DR. BURKS: I know this is a fundamental difference of opinion that all of us have, but I really would disagree that you can't go on an individual person and what they said, because I see this same thing every day in clinic about foods. Corn and whatever else causes the same behaviors that they talked about today, and scientific after scientific study has shown they're not related, but they'll have a testimonial about how taking that food out will make their behavior better.

So I really don't know that we've got that as nailed down as you might think it is, because I don't think the studies are there. It's not like there's nothing there, but it's not enough that is going to then give the public the information.

We'll say we voted on 2, there's not a causal relationship, but you need to put it on the label. That message means there's a relationship. That's what people are going to hear. That's what we're telling

them if we say that they need to put it on the label, that there is a relationship.

DR. ACUFF: Ms. Lefferts?

MS. LEFFERTS: Well, I just want to respond to that, because we talked earlier about what kind of bar we're talking about here, and we had a very high bar for question number 2. We're now not necessarily held to the same high bar here, because, again, it's science and then there's public health. And then, again, I keep coming back to that reasonable certainty of no harm, convincing evidence of reasonable certainty of no harm. I think that's more relevant in this situation.

DR. ACUFF: Dr. Blakistone?

DR. BLAKISTONE: I don't agree. I firmly believe that sound science should drive public policy, and that's what we have before us.

DR. ACUFF: Dr. Vugia?

DR. VUGIA: I think that sometimes we don't have sound science when there is an issue we have to discuss, which is why we're here. The sound science, the data aren't all in. From all the studies that have been done, some studies suggest something is going on,

and a lot of studies say that nothing is going on. And there's no definitive study that allows all of us to actually make that leap to say, yes, that there's a causal relationship.

But on the other hand, I think that the fact that most of us, if not all of us, would probably say there are more studies to be done suggests that we believe something more should be looked at regarding this issue.

So I agree that the bar for the label isn't to say there's a causal relationship. I think the label issue is what message is it that the consumers should know so they can make an informed decision, and is the information material enough for them to really be considering the information that's put on that label. I think that the fact that the FDA has used labels that contain the word "may" before recognizes the fact that not all consumers have to be affected in order for the warning to be on there.

So I think it's a tough issue in terms of what the label should contain, if the label should be used at all, but I think that it isn't the same. I don't

agree that the label requires that we have all the facts down or that all consumers are to be affected in order to consider putting a label on.

DR. ACUFF: Dr. Castellanos?

DR. CASTELLANOS: I have a question about the protection of children that we've discussed and the importance of treating them as a separate multiple class.

I wonder if we should be or if we can consider recommending labeling in those cases where the products are targeted toward children. No one will say that Froot Loops are not for grownups or things like that, but certainly there's a whole series of products that are clearly targeted to citizens who are defined as needing greater protection and in whom we have reason to have concerns that if there's going to be vulnerability, it's going to be more expressed, and the consequences will be worse.

So I don't know of that's, again, an issue on which counsel can enlighten us or if that's something we can just think about ourselves. I'm not sure we want to put labels on every single thing, but I wonder

if we should be considering about targeting.

MS. O'CONNELL: So I guess just to clarify what you're asking, you're not asking whether the statement could be directed toward children, but whether the labels could be put only on products that are --

DR. CASTELLANOS: Where children are the intended consumers.

MS. O'CONNELL: That's a really difficult thing to ask an agency or to expect an agency to be able to determine. The statute gives us the authority, again, to prevent the product from -- or the labeling from being misleading to consumers, and the way we can do that is to determine that it's not conveying information about the product.

So if a kid consumes a product that is normally marketed toward adults, I don't know how anyone can make the argument that the information wouldn't be necessary on the label of that product, as well.

Like I said yesterday, there are some warning statements that are mentioned, specific groups. So the

unpasteurized juice statement mentions -- I have the language, but -- "cause serious illness in children, elderly and persons with weakened immune systems."

So the language of a warning statement can be directed toward certain groups, but I think it would almost limit its effectiveness if it didn't reach the entire public.

DR. ACUFF: Thank you.

Dr. Burks?

DR. BURKS: I realize the question is, one, how much we agree on how much signal there is, but, also, then, what kind of level it has to get to before we would suggest a warning label.

To me, the warning label is still a pretty high bar. They have lots of other ways for the FDA to get out the right information. We want them to get out this information that we're trying to wrestle with. And I'd say a warning label has to be a pretty high bar, because that's the least effective way to educate a consumer. It's scary more than it's educational, I think.

DR. ACUFF: Mr. Waldrop?

MR. WALDROP: In response to that, putting labels at the point of purchase is actually a good way to educate consumers, and consumers are now using the nutrition facts panel as a way for information and other -- it's the point of purchase that really can -- you can get the consumer right there where they're trying to buy it.

The other point I'd raise is in terms of FDA, other methods for FDA educating consumers. I think one of the points that was raised in the petition was that some of the information on FDA's website was not getting this information out, and it was essentially saying everything is fine and there is no connection and we don't have to worry about it.

It's not part of these questions, but just in terms of FDA to think about, considering what we've talked about here, there may be ways to modify some of that information on the website so it is more relevant and more informed for the public.

DR. ACUFF: Dr. Blakistone?

DR. BLAKISTONE: As I know FDA knows, you do have a risk communication panel. That's a real good

place to go to help formulate wording to get the message out.

DR. ACUFF: Dr. Castellanos?

DR. CASTELLANOS: We're obviously all wrestling with this, and I have to say that from my perspective, the combination of the Isle of Wight data and the Southampton studies come closer to bringing me to a belief or interpretation that there are scientific data that shift the population of behaviors.

But given Dr. Stevenson's own presentation about the design elements of that study, the aggregation of compounds, never mind measures, we're probably -- I'm aware of my threshold not quite being reached, but also aware that we're closer to a threshold where a population-based awareness may need to be promulgated.

So I'm not sure what the mechanism for that is, but I think it's reasonable to convey to the agency that the prior stance that there is nothing to see here is probably not where we are; that we're not quite beyond the threshold, in part, because benzoate got put into the mix and we can't separate that out, because

the sample sizes that were seen as relatively generous turned out not to be so for trying to detect signals that are coming from subgroups within larger samples, as Dr. Weiss showed us.

So more targeted evidence is likely to be needed, but we're pretty close to that threshold, and some of us may be over it. And so that needs to be conveyed as well.

DR. ACUFF: So FDA has updated the relevant information on their website. There you go.

[Laughter.]

DR. ACUFF: Dr. Fenner-Crisp?

DR. FENNER-CRISP: I want to make one comment about website and Internet access and information access. I think we need to be mindful that while every one of us in this room have access to multiple sources of information, we still have a sizeable segment of our population who does not and/or is not capable of understanding the information on its own, but they do to go to the grocery store.

DR. ACUFF: Any further comments?

[No response.]

DR. ACUFF: Can we vote? All right. Let's look at the question.

Should additional information be disclosed on the product label of food containing certified color additives to ensure their safe use?

[Voting.]

DR. ACUFF: So it's pretty close, 43 percent yes; 57 percent no.

I noticed, before we go on to question 5, that we've had several committee members in and out, which I assume means people are getting uncomfortable.

Do we want to take a five-minute break? Okay. Let's say 10 minutes, and then we'll come back and take care of number 5.

(Whereupon, a recess was taken.)

DR. ACUFF: I think we're all here.

Dr. Voorhees has a plane to catch, and Dr. Gerba, as well. And several other requests were we're pretty sure how we're going to vote on this question. So maybe we should vote and then discuss, and then we have the voting down and then we can continue with the discussion.

Is that okay?

So let's vote. Regarding the possible association between consumption of certified color additives and hyperactivity in children, are additional studies necessary to address any questions that have been raised as to whether and under what conditions the continued use of these certified color additives is safe?

So go ahead and vote.

[Voting.]

DR. ACUFF: We can discuss while we vote.

Dr. Castellanos, just to kind of get this started, I'm intrigued by some of the comments that you made regarding the messiness of some of the studies, and maybe it's inherent in this type of -- I can't relate to that, because I work with bacteria, and I count the ones that are alive and don't count the ones that are dead, and it's pretty easy. So this is a whole different world for me. So I'd like for you to comment a little bit about that.

Can we actually do studies that will meet the level that we have to reach to do this?

DR. CASTELLANOS: So I'll bet that even in your business, there are issues relating to measurement, because that's always where the heart of the problem is. But in this field, they are certainly so central.

The good news is things are better, by far, although we still very much depend on the kind of crude ratings that have been with us since the times of Dr. Connors here in Washington in the '60s and '70s. So those are not going to go away, but there are a number of approaches that are being tested and that have been devised by investigators in this country and other parts of the world that certainly have the potential to provide other kinds of variants, and that's really kind of the key.

As we've heard about, it's nice when there's some sort of convergence. There are issues that I've become sensitized to here about the kinetics of responses. And, again, the rule is that heterogeneity rules. It can be said that there's not going to be a single factor that applies across the board. So it's going to be a question of trying to find what are the

right targets.

There have been some clues in the literature that suggest that certain kinds of cognitive tasks perhaps will have some benefit. Again, the reading of the literature by the reviewers from FDA and others has suggested a broader perspective than strictly ADHD, and that has great public health relevance in the sense that irritability is at the heart of one of the major challenges in the field, which is that there's been a more than 40-fold increase in the number of children, especially young children, who are diagnosed with having bipolar disorder over a period of about 10 years, which really strains credulity. We haven't talked about that all. But the heart of that is irritability. And so to the extent that irritability is a factor, is involved in any of these things, that becomes a major issue as well.

But, in part, because of the stimulus package, I know that there were a number of groups that were provided with some boluses of funding to either develop or refine objective measures that include very calibrated measures of activity, various aspects of

attentional performance.

One of the realities of this field is that attentional measures have tended not to be particularly useful either because they're very crude or they're highly contextual, so that's not, again, a settled issue. But there is an increasing number of ways of looking at this that would potentially be useful, but I think they would have to be, again, embedded in designs that would target some of the questions that have been suggested, some of the hypotheses that have been generated. It's not going to happen as a whole population-based approach. There's not enough money to do it that way.

DR. ACUFF: Dr. Voorhees?

DR. VOORHEES: And I totally agree with that, and Dr. Castellanos, I defer to his expertise in the running of clinical studies. I just want to say that I think, in addition, the FDA should require additional developmental neurotox studies in animals, preclinical studies that are done with the more current methodologies that would help define whether or not there is a causative relationship that can be

demonstrated under very highly controlled conditions. That might be helpful in the long run.

Thank you.

DR. ACUFF: We're missing one response, so do we all need to do it again? We're missing one individual.

MS. LEFFERTS: I didn't vote yet, and partly it's because I'm reading this question carefully and I'd like to -- I know we're all tired, and it's easy to say, of course we need more studies. But this question is saying are additional studies necessary to address basically whether and under what conditions the continued use of these certified color additives is safe. And remember that we were given what the definition of safe was.

I mean, in my mind, looking at the legal definition of safe, we don't need any additional studies to know that there is a safety issue. But yet, of course there are additional studies, scientifically, that I would very much like to see.

So this is not a no-brainer question for me at all, and I'd urge the committee to give it a little

more thought to exactly how it's worded.

DR. ACUFF: Dr. Castellanos?

DR. CASTELLANOS: I read it as asking whether the continued use of these certified color additives is safe, as well as under what circumstances.

DR. ACUFF: Any other discussion? Dr. Gray?

DR. GRAY: I have a research point I'd like to bring up, not necessarily a discussion on Ms. Lefferts' point.

I'd like to say I think that a real problem that I learned about in these last couple days and in reading this material is that the exposure assessment here is an embarrassment to FDA, I think.

FDA has a lot of knowledge, a lot of talent, a lot of ability to do exposure assessment in a very serious way, and this idea of taking the total number of pounds that are produced and dividing it by 300 million or something like that is not a helpful thing, especially -- and Dr. Voorhees brought this up several times -- when it appears, using that method, that you could in fact be getting close to levels of concern, getting close to ADIs, especially as production

increases.

I just think that a much better assessment of exposure has to be done -- something that looks at the exposures by populations helps us get a better understanding of the range of exposures in different age groups -- in order to be confident that we, in fact, are using these color additives in a safe way. So I think the exposure assessment has to be addressed in a very serious way.

DR. ACUFF: Dr. Winter?

DR. WINTER: I wholeheartedly agree with what Dr. Gray said. I'd take it a little bit further. I think there is so much data that can be gleaned from a very careful exposure assessment study. We can look at individual population age groups. We can identify the case -- if you're focusing on eight color additives, then you can get a pretty good idea of which ones are actually being consumed, at what levels. And that, I think, should allow you to design -- if you're going to work in terms of behavioral studies, it will help you design what are going to be appropriate doses.

We've heard such dramatic differences. We've

had big arguments about what's in the frosting on a cupcake right now. And I think it is an embarrassment just to take this crazy deterministic approach to come up with a very blunt number, and then say, okay, we're going to focus all our energies on this other side.

I believe that if there can be collaboration between the food dye industry and the FDA, as well as other researchers, I think it's possible to identify, predict pretty well how much various food dyes of each type are showing up in individual foods and pairing that with some decent food consumption data, such as NHANES would allow you to really make some great strides in that area that could really --

I think a lot of times people will do the behavioral assessment first and then they'll make an exposure assessment and decide whether things are appropriate or not. I think that's going backwards. We need to have a better exposure assessment to allow us to design the appropriate studies. And I think the exposure assessment is far more important than just having something that you can compare with the acceptable daily intake.

DR. ACUFF: Dr. Fenner-Crisp?

DR. FENNER-CRISP: I'll give another push for the use of NHANES. It certainly can provide -- I mean, it is the government's source of consumption data now, since it got folded in from its former separate thing that USDA ran. So that is the focus for exposure assessments. But NHANES has some other components to it as well, which is developing health profiles for the participants who also share their consumption data; so if the questionnaire is written properly, it might well be another source of information about the health profile, to include the kinds of concerns that we've been talking about the last couple of days.

Then there's another source that -- we've talked about there aren't enough samples and the problem with that. There is another structure that could be of very useful potential if the right questions are asked on its questionnaire, and that's the national children's health study that's now enrolling pregnant women to follow their children prenatally through age 20.

They will be doing repeated health profiles on

the offspring, and if one writes the questionnaire for that properly, one could pick up the changes in the health status of the offspring as they go from prenatal stage to age 20, which is the age group, encompasses the age groups we've been talking about now. And those are going to be very large numbers, too. If it's done right, it's clearly going to be a sample size that's fairly robust.

DR. CASTELLANOS: Talking 100,000 inaudible - off mic.)

DR. FENNER-CRISP: Yes. Now, if the money stays there to have that many. I mean, there's been a lot of to'ing and fro'ing about how big this thing is going to be, but it's clearly a whole lot bigger than any of these studies we've seen to date, and it will be bigger than the annual sampling that's done for NHANES.

DR. ACUFF: Dr. Fernandez?

DR. FERNANDEZ: Just following-up on what was said about the studies, I think it would be very important to evaluate them separately, the different colors, so that we can have an idea if it's one or if it's several of those that may be associated with the

things that came out in the clinical studies.

DR. ACUFF: Dr. Castellanos?

DR. CASTELLANOS: I just want to reiterate that Blue Number 1 should be put at the top of somebody's list.

DR. ACUFF: Dr. Fenner-Crisp?

DR. FENNER-CRISP: Could I expand on Dr. Voorhees' comment about the DNTs? There is currently an OECD guideline for developmental neurotoxicity, and it contains guidance on doing a number of different sets of data collection. They do not include necessarily all of the surrogates for the human behaviors that we have been talking about with respect to ADHD and other behavioral variants that we've talked about under this context.

So if one were to take that as the starting point for designing -- well, it's generally done in the rat study. It shouldn't be the complete spectrum of studies, but rather refined and tailored for the question.

There's a lot of debate about what other things could or should be added to a DNT to actually

learn enough about it, but then you have to deal with the costs and all that kind of stuff, but we won't get into that. But the point being it probably isn't sufficient as a standalone study design right now to cover all the things we're concerned about or have talked about today and yesterday.

DR. ACUFF: Further comments? Ms. Lefferts?

MS. LEFFERTS: It's been something like 30 years since the Feingold hypothesis was raised. We have a lot of double-blind studies; yet, we don't have a lot of -- we don't have the quality of data that we would like.

How many more years are going to pass until we have that kind of data? I'm very uncomfortable with this question, because it seems to imply that before we can decide whether continued use of these certified color additives is safe, we need more study. And I don't think we need more study in order to take public health measures.

Certainly, I'd love to have more studies. I'd love to have better quality studies. I'd love to have studies at more realistic dosage levels, dosage levels

that are similar to the ADI or dosage levels that are similar to what high end consumers, child consumers are consuming. But I am not in favor of additional studies if it's going to be interpreted as delaying action to protect consumers.

DR. ACUFF: Mr. Waldrop?

MR. WALDROP: Can we ask FDA if their reading it the same as Ms. Lefferts, if that's their intention with this question?

DR. ACUFF: Dr. Cheeseman, can you respond to that?

DR. CHEESEMAN: I don't know that I can. I certainly wouldn't -- if there were a reason to take action to protect consumers, we certainly wouldn't wait on studies to address questions. But there are situations -- we have one ongoing right now, which is widely known, where the agency has raised questions with regard to bisphenol A, but not questions serious enough to take regulatory action, serious enough to do testing. So it is possible for us to be in a position where testing would be necessary to address questions, but not have serious questions enough to take

regulatory action.

DR. ACUFF: Dr. Freeland-Graves?

DR. FREELAND-GRAVES: I just want to comment that I think that we do need to look at Blue Number 1. I think that is, for some of us, the top of the heap. So we think that -- I don't think all color additives are alike. I think that you need to separate them out.

DR. ACUFF: Dr. Castellanos?

DR. CASTELLANOS: I wanted to shift this a little bit in terms of design of clinical studies. We've heard about placebo-controlled, double-blind studies and those being the gold standard.

Don Klein is someone who I continue to work with and mentors me, and he recently, well, about a year or two ago, wrote a commentary in JAMA about psychopharmacology and described the way in which those studies came into being, in part, because of the FDA's requirement that there be evidence of efficacy.

But one of the problems with those studies is that it does not reveal information about individuals. It gives a signature of how a group may differ from the other group, and especially with regard to children,

it's become very difficult to enroll children into studies where there are placebo components, although the crossover tends to ameliorate that some. But, again, as we've heard, there's a lot of design issues related to that.

What Dr. Klein points out is that going back to the 1960s, an intensive design of discontinuation and repeat challenge, which, as we've heard about, is really the way in which to determine whether something is relevant to an individual, can be set up in ways that provide rigorous data.

Again, that may be one of the ways in which this can be pursued, especially with highly motivated families in whom there's either the conviction that this is important or becomes relevant to find out how seriously do we have to take this and will one M&M make a difference or not or things like that.

If that's embedded with other measures that, again, don't simply rely on subjective ratings but can provide other kinds of variants, then that's another potential mechanism of moving forward. And my understanding is that the FDA has provided guidance

that that's a design that would be acceptable, but, again, it's not out there in the field and, typically, manufacturers don't think that that's going to be good enough. But I wanted to highlight that that is another avenue with which this can be pursued.

DR. ACUFF: Good. Thanks. Other points? Okay. Mr. Waldrop, and then Ms. Lefferts.

Ms. Lefferts first. Okay.

MS. LEFFERTS: We heard from the representative from the industry that they were reluctant to take on studies for a number of reasons. They weren't clear on this topic, because of the notion that the studies would be viewed with doubt since they were funded by industry and because they were uncertain -- I believe he was saying that there was some uncertainty as to how best to proceed.

I don't think it -- it's very easy for a group of scientists to get together and come up with a wish list of all the studies that they would like to see, but are we ever going to see them? And I think we're only going to see them if they're required by the industry.

I'd just like to get that into the record and get the committee thinking about what studies we think the FDA should require of industry so that some of these outstanding questions can be resolved in a timely manner, or else our grandchildren will be sitting around this same table 60 years from now and will be talking about the same things.

DR. ACUFF: Dr. Vugia? No? Okay.

Additional comments?

[No response.]

DR. ACUFF: All right. So do you want to vote?

[Ms. Lefferts enters vote.]

DR. ACUFF: All right. So we have 93 percent yes; 7 percent no on this question.

All right. I just want to take a couple of seconds here to thank the committee. I want to thank you for all the time you put in to study these documents and prepare, because I know firsthand that took some time.

I also want to thank you for your comments and for the robust discussion that we've had. It's been

very helpful. And I hope that we provided FDA what they can use to proceed on this issue. And thank you very much to the FDA staff and all the support that they've provided.

I believe we are finished. So I'll call this meeting adjourned. Thank you.

(Whereupon, at 4:21 p.m., the meeting was adjourned.)

CERTIFICATE OF COURT REPORTER

I, Janet Evans-Watkins, do hereby certify that this transcript was prepared to the best of my ability.

I am neither counsel for, nor party to this action nor am I interested in the outcome of this action.

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Janet Evans-Watkins