of view, do you believe that the action criteria categories and major contaminant groups in those categories constitute a reasonable framework for prioritizing, in the order listed below, the regulation of filth and extraneous materials? And I won't read those lists.

Let's start again with Dr. Applebaum.

DR. APPLEBAUM: In a short answer, Mr. Chairman?

DR. BENEDICT: Yes.

DR. APPLEBAUM: Yes.

DR. BENEDICT: Thank you.

Dr. Brackett?

DR. BRACKETT: Yes.

DR. BENEDICT: Ms. Richardson?

MS. RICHARDSON: Yes. I'll reserve my comments until later.

DR. BENEDICT: We'll be happy to hear them.

Dr. Russell?

DR. RUSSELL: Yes.

DR. BENEDICT: Dr. Montville?

DR. MONTVILLE: Yes.

DR. BENEDICT: Dr. Sigman-Grant?

DR. SIGMAN-GRANT: Yes.

DR. BENEDICT: Dr. Hotchkiss?

DR. HOTCHKISS: Yes.

DR. BENEDICT: Dr. Kuzminski?

DR. KUZMINSKI: Yes.

DR. BENEDICT: Thank you. And the time now for pertinent comments is open, and Ms. Richardson would like to make the first one.

MS. RICHARDSON: Well, having seen the slide show, I will never eat anything again. And I guess being the consumer rep, I think that would be my concern, is that there doesn't seem to be the audience that there is for Ma Wong and other things here.

But if they hear that, you know, they've got this new regulatory program that is going to, as it's outlined in the executive summary, increase the protection from genuine food-borne hazards, and also I guess it means to increase the responsiveness, to express concerns of the consumers about health hazards and repugnant filth, with consumers, if they find a fragment of an insect, they don't see that as a harmless contaminant and they don't think in the terms of defect action level. To them that is repugnant filth, that there is a fragment.

And it's something that I say all the time, is what is going to be done with regards to consumer education so that they can understand how the agency made the priorities and what constitutes a real health hazard and repugnant filth versus these defect action levels?

And I guess being from Maryland, I think, you

know, the recent reports that the seafood industry in Maryland has been affected by the pfisteria scare of last year, notwithstanding the reassurances that the environment is much more protective of them, and so, you know, what is going to be done to tell the consumers what you are doing and why?

DR. BENEDICT: Would anyone else like--yes, Dr. Sigman-Grant?

DR. SIGMAN-GRANT: I'd just like to reiterate the consumer perspective that Ms. Richardson suggested. Also, the term "priority" I think from the consumer perspective might be, "Well, now you're making this a lower priority. Will less activity be focused on that issue?" If money becomes a constraint, will less focus on the aesthetic, which to the consumer in their mind is just as important as the health hazard, if it's their food that's being affected.

DR. BENEDICT: All right. Mr. Harris, yes, please.

MR. HARRIS: Now I do have some comments. I think we've arrived at a point where we need to recognize that many of the defect action levels were not scientifically arrived at. I know that because I'd say maybe almost half of them are mine, and they were arrived at by a series of telephone calls around the agency between myself or Bill Eisenberg and a fellow named Kenneth Kirk, and I think we

need to recognize that these people are going to--the micro group are going to need some funds to get a lot of this work on a good, sound scientific basis.

Thank you.

DR. BENEDICT: Thank you. So this ends this portion of the discussion, and we're going to break for lunch, but before we do, I want to thank both of our presenters for very clear, very educational presentations, and I know that they helped my understanding of the topic, and I can see they helped everyone else, as well.

There will be a, for lack of a better term--I'm making this one up--a get-acquainted lunch for the Food Advisory Committee members in the break room, so that you can begin to bond. And that will begin probably as soon as you can wander down there. We will reconvene promptly at 1:15. The meeting will begin with you or without you. Thank you very much.

[Whereupon, at 11:45 a.m., the committee recessed, to reconvene at 1:15 p.m. the same day.]

A F T E R N O O N S E S S I O N

1:15 p.m.

DR. BENEDICT: Okay, it is the time to begin, and so we shall do that. This afternoon we will be discussing patulin, and we will have several presentations, as you can see from your agenda, by people associated with CFSAN; and rather than introducing ourselves all around again, we will just introduce them as they come up.

But I would like to acknowledge Mr. Alex Liberman, sitting over in the corner. Wave, Alex. He is the attorney for patulin, and he'll be here to make sure we don't mess up, discuss the wrong things, or discuss the right things improperly, and so he will pipe up at the time that would be appropriate.

So the way this will go is, we'll have an introduction by Dr. Michael Kashtock, who is Chief of Regulation and Enforcement. Then we'll do an overview by Dr. Vincent Zenger. The toxicology will be discussed by Dr. Michael Bolger. Exposure, we will go back to Dr. Vincent Zenger, and then a summary by Dr. Troxell.

Then there'll be time for questions from the committee. Take a break. There'll be an open public hearing, and we have one and maybe two people who wish to speak, and we're going to have--the questions then will take place after that.

The focus of the discussion is establishment of an action level for patulin in apple juice and apple juice containing products.

The charge, you're being asked to evaluate the adequacy of the science supporting the establishment of an action level for patulin in apple juice and apple juice containing products.

And the questions that you'll be asked are in your documents: if the available scientific data support the establishment of an action level for patulin; and if so, based on your knowledge and expertise and the data that have been presented, would 50 ppb be sufficient to protect public health.

So we'll hear from our speakers, have our discussions, and then address those questions. So then let's begin with Dr. Michael Kashtock, Chief, Regulations and Enforcement Branch, Office of Plant and Dietary Foods and Beverages, CFSAN, who will give us our introduction.

There should be something there. There is a microphone, is there not, a traveling one?

DR. KASHTOCK: Good afternoon. I am Dr. Michael Kashtock, and I will provide the introduction.

One of the major areas of focus of FDA's regulatory program for foods is the area of contaminants. Contaminants can include heavy metals, such as lead and

arsenic; synthetic organic chemicals, such as PCBs; and mycotoxins, such as aflatoxin.

In some cases the origin of a contaminant in food can be traced back to past industrial or agricultural activities and the resulting effect of these activities on the environment in which food is grown. However, in the case of mycotoxins, including the subject of today's meeting, patulin, the origin of the contaminant is molds, which are intimately associated with foods such as grain and fruit in the natural environment in which foods are grown. Mycotoxins are produced by molds that can occur on foods in nature.

While the occurrence of molds such as Aspergillus, Fuserium and Penicillium cannot be avoided on certain foods, mycotoxin levels in such foods can be controlled by avoiding the use of foodstuffs that can be associated with significant mold growth. Avoidance of the use of spoiled or damaged apples can provide substantial control of patulin levels in apple juice.

As was just stated, the focus of today's discussion is the establishment of an action level for the mycotoxin patulin in apple juice and apple juice containing products. Action levels are a form of FDA guidance which state levels of a contaminant in a food at which FDA believes that, based upon the science, FDA could support

regulatory action against the food containing the contaminant to protect the public health.

An action level, if established for patulin, would be the second FDA action level addressing a mycotoxin in food. Action levels for aflatoxin in food and animal feed were originally established in the late 1960s.

Not all mycotoxins of which we are aware are the subject of action levels, because some are not likely to occur in foods at levels that would cause a public health concern. However, when there is a potential for a mycotoxin's presence in food to raise concerns, FDA considers establishing an action level to provide for public health protection and to give the food industry guidance to use in designing and implementing appropriate controls, if not already in place, to ensure the safety of the food produced.

We expect that action levels for mycotoxins in food--excuse me--we expect that levels of mycotoxins in foods will not exceed action levels. As part of our compliance program for contaminants in foods, we monitor the food supply for levels of mycotoxins, and we are prepared to take enforcement action to protect the public health.

We intend to establish an action level for patulin in apple juice and products that contain apple juice because, as you will see, data have shown that levels of

patulin which we consider to be of concern have occurred in these products. When FDA has considered establishing action levels for contaminants, regardless of the type or origin of the contaminant, we have frequently utilized the safety assessment approach in which the following considerations are taken into account:

Number one, we assess the risk posed by the contaminant.

Number two, we establish the level of consumption of the foods in which the contaminant could occur.

Number three, based upon consumption, we estimate exposure to the contaminant.

Number four, given the risk posed by the contaminant and the exposure to the contaminant, we establish a level of the contaminant in the subject food which, if not exceeded, would ensure that the food is safe. I'll simplistically refer to this as a desirable maximum contaminant level, and this is not always one level. It can be levels, depending upon the degree of conservatism taken in the safety assessment approach--a strict conservative approach, a less conservative approach--so we don't always come up with one level.

And then, number five, the achievability of the desired MCL. We then ask, is control of the contaminant not to exceed the desirable level achievable under the

conditions in which foods are grown and produced?

If the answer to the last question is yes, that the desirable MCL is achievable, we have the best possible outcome. We are not limited in our ability to provide the desirable level of public health protection by unavoidability concerns regarding the presence of the contaminant in or on foods.

The succeeding presenters will take you through our analysis for patulin as it touches upon each of these considerations, and we will lay out for this committee why we have determined that the 50 ppb level--that the 50 ppb action level we are asking you to consider is protective of the public health and is achievable.

Following my presentation, you will hear from Dr. Vincent Zenger who, as stated, will give you an overview. Dr. Michael Bolger will discuss the toxicology of patulin; Dr. Zenger again will discuss exposure; and, finally, Dr. Terry Troxell will discuss the rationale for the 50 ppb action level and provide a summarization.

That is the introduction. I thank you for your attention, and I'm going to make an appointment with the eye doctor.

DR. BENEDICT: Okay. We'll now hear from Dr. Vincent Zenger, Division of Product Policy, Office of Pre-Market Approval, CFSAN. He will give us the overview of

patulin.

DR. ZENGER: Thank you. My purpose here this morning is to give you just the briefest overview of what patulin is. Next slide, please.

Patulin is a small molecular weight secondary metabolite of fungi. You can see here its structure. I'll just take the laser pointer here. Just one notable feature here is the lactone structure of this particular metabolite, which makes it susceptible to certain chemical reactions. One which I'll mention is its reaction with cystine. And cysteine, the sulfur residue here would be attached here at this four position, and a hydrogen molecule would be added or a hydrogen atom would be added up here. So that's the reaction that I'll talk about in just a second. Go ahead, next slide.

Just a brief history of patulin. Patulin is really not that well studied. It was first isolated in 1944 from Penicillium claviforme, and was named clavacin at that point. In 1943 it was also found in Penicillium patulum and sort of renamed. In 1949 the chemical structure was elucidated, and in 1952 and subsequently it was tested briefly as an antibacterial, antibiotic product, but that was given up for toxicological reasons. And just as a time point, I put in 1981, which was when sort of the study that we're using mostly to rely on to establish the safety levels

and so forth was done, in 1981. Next slide.

This is a list of a few of the fungi which are known to produce patulin. Most of these here are Penicillium. If you go on to the next slide, it's also shown to be produced by certain other species, Aspergillus, notably, and a couple which I hesitate to try to name. Go ahead, next slide.

Some of the chemical characteristics of patulin, it's soluble in a number of solvents, including water, ethanol, acetone, amyl acetate. It's known to be stable in acid solutions but unstable in alkaline solutions, and in alkaline solutions it's been shown to lose its biological activity. It's also reported to be destroyed in fermenting of various products which contain patulin, like apple juice, for instance. It's only moderately destroyed by thermal processing. And, as I mentioned before, it also reacts with sulfhydryl groups and possibly, although it hasn't been strictly shown, with some amino acid groups of proteins. Next slide.

Patulin has been found on a number of different kinds of fruit, apples, peaches, pears, bananas, grapes and melons; also on various vegetables, peppers, cucumbers, carrots; and also on animal feedstuffs; but has not been reported as being found on anything that didn't have rotten components or the actual fungi. Go ahead, next slide.

For interest, I did list here from the literature reported patulin levels that were in the literature from various studies. As you can see, they range from zero up to 45,000 micrograms per kilogram, which is pretty high.

And even in the recent studies, here was one done in 1988, you can see patulin levels here ranging from 7 to 376 micrograms, and I'll mention in that study that of the 200 samples, about 50 percent were above 50 micrograms per kilogram contamination level. So even in this day and age, we're still seeing high contamination levels in apple juice, and a lot of this variation probably has to do with the way the apple juice was produced and the techniques that were used in production. Next slide.

One of the reasons why we're not considering other products at this time is that problems in other products haven't been demonstrated. And one way you can look at this, this is solid apple-based products. This is years. This information was submitted as part of a letter to WHO on what position should be taken on patulin. But if you look here at the sample results, very few if any of the products that resulted from apple solids were found to contain patulin at greater than 50 micrograms per kilogram.

So if you can imagine apple juice being contaminated, you would likely suspect that apple products themselves might be contaminated, but that isn't the case.

Now, there are other reasons why you might suspect other things, like peaches and so forth, if consumed as a solid, wouldn't be a source of patulin, and those have to do with organoleptic reasons and stuff. You wouldn't eat a rotten piece of fruit. So our concern at this point is strictly with apple juice and apple juice containing products.

There also have been a small number of studies looking for patulin in other products like apple juice. In several small studies of very small numbers of samples, patulin hasn't been reported above the detection level of the study. And, again, that probably goes back to the stability of patulin in various types of products, its reaction with sulfhydryl groups and so forth.

So there seems to be, if it was contaminated, a factor that reduces patulin in those products. And I will mention that the reaction product with cysteine, patulin with cysteine has very decreased toxicological properties compared with the patulin product itself, although the metabolites of patulin in human or animal studies haven't been strictly studied. Next slide.

And I just wanted to make a quick mention of analysis for patulin. There are a number of analytical procedures available to analyze patulin. This is one that's recently been developed with the help of FDA. It's become an AOAC method. Basically, patulin is extracted in ethyl

acetate and cleaned up with extraction of sodium carbonate, then spin-dried, and then it's run on a reversed-phase liquid chromatography column, and this whole procedure takes approximately a day, depending on how many samples you have.

So a method of analysis is available. In fact, there are quite a few methods. This one has a detection limit of approximately 5 ppb. And so these methods are available for those that want to analyze for patulin.

So that concludes my brief overview of the patulin molecule.

DR. BENEDICT: Thank you, Dr. Zenger.

We're going to hear from Dr. Michael Bolger. Dr. Bolger, if you need to read something, we can get some light, or you could remain seated if you like, whatever is comfortable for you. Make your choice.

Dr. Bolger is Chief, Contaminant Standards Monitoring and Program Branch, OPDFB, CFSAN. He will be describing the toxicology for us.

DR. BOLGER: While he's getting ready, I want to over the next 20 minutes just give you a very brief overview of what we know about the toxicology of patulin. I'm only going to highlight significant end points that have been assessed in various animal bioassays and significant studies. I don't have the time, and I don't think you would want me to go through an hour lecture on this. And

everything I will cover here is in the package that you received as part of the narrative presentation on the toxicology of patulin.

Let me just have the first slide. I want to acknowledge the invaluable contributions of Dr. Sara Henry, who was of great assistance in helping me put this package together. In fact, Sara would have been the one making this presentation, not me, but she was committed to attend and make a presentation at a conference this week, so she could not be here. Next slide, please.

And you've already seen the structure of patulin, so we don't need to go over that again. What I would like to do is briefly go over, starting with--in terms of what we know about acute exposure in rodents. I believe in your package it says that the data on this indicates moderate toxicity. I think that's something of a slight understatement. I think there's a range that varies anywhere from moderate to high toxicity.

Remember, LD50 studies are rather imprecise measures of acute toxicity, because again we're assessing lethality here. But in some tests they have been actually determined to be in what we would deem to be a highly toxic range for LD50s.

In terms of short-term and subchronic exposure studies, I'm going to focus on immunotoxicity studies that

have been done, on the mutagenesis studies that have been done, on the teratogenic studies that have been done, and then I will finish up with an overview of several key studies that have been done in terms of chronic exposure and touch upon the issue of carcinogenic potential of patulin. Next slide.

In terms of studies done to assess immune function, effects are mixed, with some immunological response measures reduced and others stimulated. Well, this is not surprising. I think you can say that probably for many, many things where you get sort of a mixed bag in terms of sometimes, depending on the species you're assessing, depending on the end point you're measuring, whether you're looking at cell or humoral immunity, sometimes the studies don't always give you a consistent picture.

I think the most important thing, thought, to keep in mind, and I'll get to this at the very end of this, is that you really have to--I think the most important thing to keep in mind is the dose levels that have been used in these studies and how they relate to what we know in terms of human exposure levels.

So in a study in 1986 by Sorenson, macrophage phagocytic function was impaired. In a study by Escoula in 1988, response to several immunological challenges, to phytohemagglutinin and concanavalin A, were decreased, and

serum immunoglobulin IgA and IgM levels were lowered, and lymphocyte counts were decreased. Next slide.

In this study they also noticed an increased neutrophile count occurred in mice, increasing resistance to Candida albicans infection. Now in a study by Becci which I will get to later on, which is really the key study in terms of identifying the study, in terms of describing a safe level of exposure, in this chronic study they noted lymphocytopenia and neutrophilia was assessed and no effects were noted.

Now I think the most important study here is the very recent study from last year, by Llewellyn in 1998, last year, in which female B6C3F1 mice were assessed at six different dose levels, and these dose levels were much lower than the dose levels used in the previous studies, and are dose levels much more consistent with what we know about human exposure levels. And in a variety of end points and assessment techniques, they were not able to detect any ability of patulin to affect cell-mediated or humoral immune responses. Next slide, please.

Now in terms of mutagenic effects, again, when you look at the body of information, and I would like to note that there is a fairly robust data set in terms of the number of different studies that have been used, end points, both in terms of bacterial, mammalian systems, both in vitro

and in vivo, and something like the immunological area you sort of get a mixed message, a mixed picture here, where overall you get sort of an impression that there is an equivocal presentation of results.

But I think you really have to sort of step back and look at what is it in terms of the bacterial systems versus the mammalian systems. And then when you look at that, it's--you get the overall, general impression that in terms of bacterial systems the responses are generally negative. In mammalian systems they tend to be somewhat on the positive side.

So in Salmonella assay systems, you know, the well known Ames assay, both in vitro and in vivo, no mutagenic activity was noted in a variety of studies. Chromosomal effects, either damage or an increase in sister chromatid exchange, have been recorded in mammalian cells in culture. In a hamster bone marrow cell test system, chromosomal breakage was demonstrated.

Now, overall there is no convincing evidence of a germ cell mutagenic potential in three studies in rodents. But as I said, when you look at overall potential, it's somewhat equivocal but it really depends on whether you're looking at bacterial or mammalian test systems. Next slide, please.

In terms of teratogenic effects, patulin has been

assayed in the NMRI mouse assay system using five different dose levels, I.P. or per oral, and this is a study in 1990 by Roll in which they found an elevated level of cleft palate.

In a study by Dailey in 1977 in the Sprague-Dawley rat, at one dose level this showed an increase in resorptions in the F1 litters but not in the F2 generation, and the average weight of male fetuses in the F2 generation was significantly less than controls. You will note that when I talk about the Becci study later on, the significant decrease in body weight in the males was a very telling effect in terms of patulin exposure.

In a study in Charles River CD1 rats, at two dose levels there was a significant decrease in the average fetal body weight at the lower dose, and all implanted embryos were absorbed at the highest doses. This is a study by Reddy in 1978.

Now the two key chronic studies are the study by Osswald and Becci, and Osswald's study was published in 1978 in the SPF Sprague-Dawley rat, where the animals were gavaged twice weekly. There was a single dose level used for four weeks at 1 mg per kg, and then the dosage was increased to 2.5 mg per kg of body weight for the following 70 weeks. The total dose was 358 mg per kg of body weight. And no effects were noted on weight gain or survival, and

there was no significant difference in tumor incidence, and I'll come back to this tumor incidence issue in a few minutes. Next slide.

Now the Becci study of 1981 was a study that was done with the FDRL Wistar rat, both sexes, using three dose levels of .1, .5, and 1.5 mg per kg of body weight per day of patulin, three times a week for 24 months. So I just want to point this out, this was not a daily exposure, this was three times a week. So the corresponding weekly doses would be .3, 1.5, 4.5 mg per kg of body weight per week.

Now the male body weights were reduced in both the mid- and high-dose levels. The female body weights were comparable in all dose groups, so there was a differential effect in terms of effects on the sexes here. There was no difference in tumor incidence that was observed. Again, I will come back to this in a few minutes. But there was a substantial mortality in both sexes at the high dose groups, and I will show this in the following two slides.

The first slide is the mortality data from the Becci study for the male rats, and you can see that for the high-dose group, which is these solid boxes, there is a rather substantial increase in mortality occurring early on. This is time in months, and this is percent survival, so you can see in terms of this first time point evaluation, which I believe is about three months, there was a significant

occurrence of mortality in the high-dose group.

The other dose groups did not show this increased mortality until later on in the study, but as you can see, halfway through the study these other--the two lower dose groups, the low and mid-dose groups also noted a significant increase in mortality as compared to the controls. Next slide, please.

This is the mortality data for the females. There is a difference here, now, in terms of what was happening in terms of the males. Again, I'll go back to some of the observations I noted in some of the other, particularly like the teratology studies, where there was a sex difference in the effect. At this early time point there was not a demonstrable difference particularly in the high-dose group, but as the study went along, you started to see an increase in mortality in the high-dose females.

The low-dose females, again, they did not show the same increase in mortality until later on in the study. But again, as in the latter half of this study, they too were showing a significant increase in mortality from the control groups, which are the open circles.

Now in terms of the carcinogenic potential of patulin, the Becci study was actually a study that was designed to address not only the chronic toxicity of patulin but also the carcinogenic potential. But because of the

significant mortality that occurred, and the clear--and we clearly saw that the maximum tolerated dose had been exceeded, and the fact that you saw a substantial effect on body weights early on in the study, it really did limit the ability of that study to answer the particular question about the carcinogenic potential of patulin.

The Osswald study is also limited because it was only a single dose study, and I think when you compare how we look at bioassays, long-term bioassays today, it really does fall short of the mark in terms of how we do bioassays.

So in 1986 the Interagency Agency for Registry on Cancer concluded that there is inadequate evidence for the carcinogenicity of patulin in experimental animals. No evaluation could be made of the carcinogenicity of patulin in humans. And that is because even today we have--there are no studies that have been done to look at this particular end point in any human population.

I would have to add, too, that--can we go to the next slide--that the Joint Expert Committee on Food Additives of the World Health Organization reached a similar conclusion in their most recent evaluation of 1996, and in fact in 1990 in their previous evaluation of patulin had asked that a study be done because they felt, in looking at these two studies, they were just simply not adequate to answer their questions.

Now in terms of mechanism of toxicity, and some of this Mitch has already touched upon, but I want to briefly go over it because I think it's kind of key in terms of how one looks at these observations noted in terms of immuno effects, teratogenic effects. As Mitch said, patulin probably involves binding the sulfhydryl groups--it has a real affinity for them--and to a lesser extent amino groups of amino acids and proteins in the plasma membrane and cytoplasm.

And as a result, several enzymes, probably many enzymes, have the potential to be inhibited. We know, for instance, that cellular glutathione is bound by patulin. There's a--studies have shown that the flow of ions, particularly sodium, potassium and calcium, across the plasma membrane is severely compromised. Cellular respiration is decreased, perhaps by disruption of the mitochondrial function, probably involving some of these mechanisms. Next slide.

The chronology of cellular injury caused by patulin, there is a simultaneous expression of gap junction mediated intercellular communication and glutathione depletion, followed by reactive oxygen species generation, followed by mitochondrial membrane depolarization, which I just touched upon, and simultaneous increase in calcium, cytoplasmic acidification, and depolarization in the plasma

membrane. The type of damage you see in individual cell types really will influence the pathological manifestations you see.

So, as an overall summary in terms of the LD50 studies--and again, I've just picked out a few of the studies, there are any number of studies that one could include in a rather extensive list--in terms of the dose levels that have been identified as LD50s, one would deem these to be in the highly to moderately toxic range. Escoula noted immune suppression effects in using dose levels in the mg per kg of body weight range. In a very recent study by Llewellyn using a broader range of doses and much lower dose ranges, no immune effects were noted.

In terms of the teratogenic potential, cleft palate was noted in a study by Roll in 1990. Next slide. I already touched upon the Osswald study, where no neoplasms were noted, but again I pointed out the shortcomings in terms of that conclusion.

In terms of the Becci study, which, when one looks through the entire database available on patulin, this is the study that has the effects that are most prominent where there is an observable "no observed effect" level at the lowest dose level. One can describe a "no observed effect" level in terms of looking at teratogenic, immunological studies, but they are at higher dose levels.

So if one is going to be describing a bright line, safe level of exposure, the Becci study is the study that one would focus on, and in fact that's what the Joint Expert Committee on Food Additives concluded, that in terms of describing a safe level of exposure, the "no observed effect" level was--and actually this is backwards. I just realized that these dose levels are backwards. Reverse this. The increased mortality is 1.5, decreased body weight was .5, so that's all right, and "no observed effect" level was 0.5 mg per kg of body weight. Next slide.

So in terms of the description of the safe level, or what we would call in terms of a contaminant, the term that's used, the tolerable daily intake figure, the provisional maximum tolerable daily intake that was determined was 0.43 micrograms per kg of body weight per day, or 3.01 micrograms per kg of body weight per week.

This is based on the "no observed effect" level at the lowest dose level, where we had an ingested dose of 43 micrograms per kg of body weight per day. Remember that the lowest dose level was administered, over seven days, only three times during the seven-day period, so we adjusted it to a daily dose level. And this, the derivation of the provision maximum tolerable daily intake, involves the use of two 10-fold safety or uncertainty factors, one 10-fold factor to account for interspecies extrapolation, one 10-

fold factor to account for intraspecies sensitivity.

And I believe that's it, and that concludes my presentation.

DR. BENEDICT: Thank you. Well ahead of schedule, we'll now hear from Dr. Zenger on exposure levels.

DR. ZENGER: Thank you, Dr. Bolger.

As part of our safety assessment, we estimated the exposure that one might get to patulin. In estimating our exposure, we used a Monte Carlo method for calculating the exposure. This Monte Carlo method needs two key pieces of information: patulin levels in food, and also the estimated food intake, in this case estimated food intake to apple juice. Next.

Several key features of the Monte Carlo method are that it allows for the calculation of exposures at more than one intake level, and it allows for calculations based on intake of more than one food. Next.

And some assumptions made in the Monte Carlo analysis are that food intakes are defined by a distribution of values, not just the mean food intake value; that the frequencies in occasions of eating are random; and that the food selections themselves are also random, so the various foods that are being analyzed, one could hypothesize that a person might take, you know, more than one of each food type per day. Next.

Just as an example of how this works, what you would do as part of the calculation, you would take the food you were interested in from this distribution of food intake estimates. The program picks a point based on this likelihood distribution here. It goes over to the, in this case the contamination level for that food, and picks again from this probability distribution a contamination level. It multiplies those two components, then moves to another food, does the same calculation, sums the intake of the contaminant, and plots that intake level into a probability distribution here. And from that distribution you can determine the mean intake of the contaminant as well as, for instance, the 90th percentile intake.

This iteration here is done, you know, depending on how fast you run your computer or what not, you can do 100,000 or 200,000 iterations here to get a very defined probability distribution. Next.

As I said, one of the key features of doing the exposure is having some idea of the patulin level. In calculating the patulin level, we relied on 2,977 samples. These samples came from several different sources. One was from the FDA compliance program, where we go out and analyze apple juice samples for a number of different reasons. Some of these are compliance, and some were done as part of our market survey analysis.

And I might just mention that these compliance samples would include rejected lots, or lots that had patulin levels that were too high, even given that we have no established level at this point. And also we got some data which was supplied by the National Food Processors Association, approximately, I think it was 650 data points from their analysis. So that is where we get our estimates of patulin in apple juice.

For the juice intake data, we rely on the USDA Nationwide Food Consumption Survey, and this data set was the one from '94 to '96. Several key features of this data are the fact that it's based on a two-day recall of consumers. It's not a long-term survey of food consumption. It's, like I say, very short, a two-day survey. Next.

And the food categories that we used in our analysis were juices, natural, canned and bottled; frozen juices; drinks and ades that contain more than 10 percent natural juice; and baby food, processed juice drinks, but excluded from it the solids, apple solids, as I explained from previously why we thought that wasn't necessary. Go ahead.

When we ran our analysis, we were particularly concerned about children. Children have a very high apple juice to volume ratio, intake ratio, high intake to weight, so in conducting our analysis we were particularly concerned

with protecting the safety of children. So in our analysis, we broke our analysis down into three separate categories: consumers of all ages; consumers one to two years old; and consumers less than one year old.

And we did our calculation, here we get the mean exposure in micrograms per person per day. Here is the mean intake values in grams per person per day. And we also, as I said, did our analysis at the 90th percentile. Go on to the next slide.

And this--can you go back one?--and this analysis here was based on the fact that we excluded no samples from our analysis, so all of our samples, regardless of patulin level, were included in this particular analysis here to get these results. Next.

We ran the analysis again, and this time excluded from our patulin levels any sample that had a greater than 50 ppb concentration of patulin in the juice, ran our calculation again, and as you can see, the mean exposure in micrograms per person per day dropped pretty significantly. Can we go on?

And just to note, in our calculations, in converting to micrograms per kilograms body weight per day, we used the standard weights: the all-age-group, 64 kilograms; one- to two-year-olds were 12 kilograms; and less than one were considered 8 kilograms. This is our standard

sort of weights that we use. Go on.

And just to reiterate what Dr. Bolger said, in reviewing our analysis we considered the JECFA PTDI, the provisional tolerable daily intake which was calculated by the Joint FAO/WHO Expert Committee on Food Additives in 1995 in their 44th report. In that report they established the PTDI at 0.43 micrograms per kilogram body weight per day, and as Dr. Bolger mentioned, this calculation has a 100-fold safety factor into it, factored into it. And I will mention that this calculation was based on a long-term exposure to patulin, not a short-term exposure. Okay, next.

When we converted our analysis to a microgram per kilogram body weight per day, this is our results. Again, here with no juice excluded, you can see that for all ages we're actually already below the .43, but when one looks at say for instance the 90th percentile eater, that's one- to two-year-old, we are above, in this case above the PTDI for patulin, and also for the less than one-year-old. All right, you can go on.

Again, when we run the analysis where we have excluded juice samples with greater than 50 micrograms per kilogram and look at our analysis, here you can see again we have dropped the mean exposure in micrograms per kilogram per day by approximately a factor of three, and this is pretty much across the board for all the analysis, and here

you can see the 90th percentile eater from a one- to two-year-old drop below the PTDI that JECFA had established.

And just so you can compare the numbers, here I put both tables on the same graph, and again you can get the idea that we have dropped in the 90th percentile eaters by a factor of three, and also for the mean eaters by a factor of three. So that is a pretty significant reduction in exposure. Go ahead.

And part of our analysis we also feel has built-in conservatisms. One would be, an overall improvement in patulin levels is not taken into account in our evaluation, and if we go on to the next slide, I can tell you what I mean by that.

This data was taken from the British Ministry, where they in 1992 implemented a regulation limiting patulin levels. As you can see, prior to 1992 they had a significant number of samples here, the pink and red being samples that were above 50 micrograms per kilogram. Okay? But as their program became--came on line, you can see that the distribution in patulin levels shifted to much lower levels, in fact much lower than the 50 which was their limit that they implemented.

So we think if we implement our level, that we would see hopefully a significant shifting in patulin levels, not just a chopping off of levels above 50. We'll

see a shift by the producers to lower levels of patulin. That was not taken into account in our estimate of exposure. Okay, if we go on the next slide.

Okay, there are also some conservative features that are built into the Monte Carlo method, those being in this case that we essentially considered all the foods to have the same contamination levels. There is some evidence to suggest, and several authors have reported this in their analysis of samples, that samples that were intended for children seem to have much lower levels than patulin--than juice that was intended for the general public, particularly in these small packages that were designed particularly for children. Okay, that was not taken into account in our analysis because we don't have that data.

And again, as I and Dr. Bolger both mentioned, there is a 100-fold safety factor built into the PTDI that we're using, and the PTDI was based on a long-term exposure. And I just want to reiterate that the exposure analysis that we did was based on two-day recall surveys of eaters, and it's very hard to extrapolate from a two-day survey what a long-term intake of apple juice would be, and so we think that that would add another conservatism to our model. Okay.

And so our tentative conclusion, based on our analysis, is that the proposed maximum limit for patulin of 50 micrograms per kilogram in apple juice and apple juice

containing products would be able--would protect the public health to a level of a reasonable certainty of no harm, which is our standard that we have. So I believe that's it. Thank you.

DR. BENEDICT: Thank you.

And finally we'll hear from Dr. Troxell, who is Director of the Office of Plant and Dairy Foods and Beverages of CFSAN. He'll give us a summarization.

DR. TROXELL: Well, I'm afraid I'm going to reiterate some of the things that were already said, but I only have four pages of large type reiteration, so bear with me.

One of my primary roles at the FDA is as a risk manager. What I want to do is give you an FDA risk manager's perspective on this issue.

As chemical contaminants go, patulin is relatively easy for a risk manager. As a rule of thumb, when a contaminant comes onto our radar screen as a significant issue, the science is often inadequate, putting the risk manager into the situation of decision-making in uncertainty.

In the case of patulin, there is a body of data, including a lifetime study with a "no adverse effect" level. Furthermore, an international body of experts, JECFA, has used that study to establish a provisional tolerable daily

intake. We have carefully evaluated the literature and agree with JECFA's evaluation.

Secondly, the analysis of contaminants usually does not work using the simple safety assessment approach. For example, lead is a good case of a chemical contaminant for which safety assessment has not worked because levels of exposure exceed the safe level. In those cases, usually more sophisticated procedures such as probabilistic quantitative risk assessments are necessary, and decisions need to be made to achieve the greatest public health protection in the light of the unavoidability of the contaminant.

In the case of patulin, we believe the safety assessment approach is sufficient. The safety assessment approach is a time-honored method used for evaluating safety of chemicals, including both contaminants and additives. We use it where we can for chemical contaminants, as it is simple and we can screen relatively quickly those situations where the level of a chemical contaminant in a food is safe, that is, meets a negligible risk. We believe that patulin would present a negligible risk at the 50 ppb action level.

In a safety assessment, whether for a contaminant or a food additive, normally a safety factor of 100 is used to extrapolate from the highest "no adverse effect" level of a chronic study to an acceptable or tolerable daily intake.

This is then compared to an estimated daily intake. The agency typically uses 90th percentile short-term intake for the estimated exposure. We certainly would use long-term intake if we had it, but such data have not been developed.

This procedure, taken as a whole, is considered conservative and robust and is expected to protect consumers to a reasonable certainty of no harm. The exposure estimate normally used for comparison is the all ages exposure. It more accurately represents the two-day exposures experienced throughout a lifetime, which is the relevant time scale for considering chronic studies. In the case of patulin, for the 50 ppb action level, our analysis indicates there is an extra five-fold safety factor for a total of 500-fold safety factor.

Of course, we recognize that exposure is more heavily weighted toward childhood years. Not only do children consume more on the average, but their body weight is lower, thus leading to relatively higher exposure per kilogram body weight. In order to determine if there was an adequate margin of safety for children, we evaluated their exposure and found that it does not exceed the PTDI. Thus, even at the most highly exposed lifetime interval, childhood, there is a 100-fold safety factor at the 50 ppb action level.

Therefore, we believe an action level of 50 would

assure that the patulin that may occur in apple juice is safe. We have found in surveys, as you have heard, of products, that on the order of 20 percent of the samples exceed 50 ppb. As you have seen, establishment of a 50 ppb action level reduces the estimated exposure by roughly a factor of three.

We believe, however, that actual levels in consumer products are significantly lower than found in the surveys, because many of these samples were industry samples used to determine the suitability of the juice before processing, and were rejected if high, and others were compliance samples which are biased high. Even though many survey samples exceeded 50, we expect it is feasible to routinely produce apple juice with levels below 50 ppb.

Both the National Food Processors Association and the Processed Apples Institute have requested the FDA to establish a limit of 50 ppb. Various European countries, including the U.K., as Vince has pointed out, have established 50 ppb levels. Patulin has also been under consideration in the Codex Committee on Food Additives and Contaminants for three years, and the level of 50 ppb was forwarded this year for adoption by the Codex Alimentarius Commission at step five of the eight-step process.

In my experience as alternate head of the U.S. delegation to the CCFAC, the Food Additives and Contaminants

Committee, with principal responsibility for contaminants, there is no significant dispute that a 50 ppb level is feasible by using the simple preventive control of assuring that sound fruit is used. While we recognize that patulin cannot be totally avoided by preventive controls due to its occurrence with minor blemishes and hidden rot, 50 ppb is feasible, and based on our analysis, we believe it is sufficient to protect public health.

In our analysis to determine the effects of a 50 ppb limit, we simply excluded all samples exceeding that. To comply with the action level, we expect manufacturers to implement preventive control measures, such as culling, to assure that finished product meets the action level.

We expect, therefore, that the distribution levels would be shifted to levels substantially lower than 50 ppb on the average. I think Dr. Zenger's illustration of the U.K. situation further suggests that would also happen in the U.S. Furthermore, in our notice issuing the action level, the agency will recommend that proactive steps be taken to control patulin in product, to reduce it to the greatest extent feasible.

Finally, after issuing the limit, the agency will monitor compliance. This monitoring will also provide an after-the-fact patulin level distribution, a new patulin level distribution curve. We therefore will have a means to

verify that the limit is resulting in the expected reduction in exposure, and we can take corrective action if needed.

That concludes my remarks, and that concludes our presentation. Thank you.

DR. BENEDICT: Thank you, all of you, for very nice presentations.

We enter into the section where we will ask questions of any of the speakers, and I ask you to direct your questions to a speaker using their name, each of which is visible to you, so that everything can be on the record.

The discussion really is the discussion of action levels and things like that. We are not really concerned in this discussion with regulatory issues. The question that we want to answer has to do with, should it be, and should it be this level.

So we'll open the floor for questions from anyone from the panel. Dr. Sigman-Grant?

DR. SIGMAN-GRANT: Yes. My questions are to Dr. Zenger, mainly about the exposure and how you calculated it. Do you know what the range of intake might have been, particularly with the children? The mean seems a little bit low to me. Do you have any idea about the range?

DR. ZENGER: Well, just thinking back, I think--well, the 90th percentile was, what, around 500, I think, for the children. I that what you're talking about, the

children's exposure?

DR. SIGMAN-GRANT: Yes.

DR. ZENGER: Yes, I think that was the 90th percentile. I don't recall what the 99th percentile was off the top of my head.

DR. SIGMAN-GRANT: The reason I'm asking, because obviously some children, especially the young ones, drink large amounts of apple--

DR. ZENGER: Again, I think that's a little bit confusing because, like I said, based on that two-day survey data, I mean it would be hard to imagine someone drinking huge quantities. Maybe over a short period of time for--you know, that would be possible, but over the lifetime, which is really our major concern, you know, it doesn't seem that we have the data to support that, you know, they'd have a really high intake.

DR. SIGMAN-GRANT: Well, that's the national food consumption the CSFII for the three years. My next question is, in '89 was an Alar scare, and a lot of consumers decreased their consumption of apple juice, particularly moms serving children. I don't know if this has slowly increased in volume--if volume has slowly increased over the years in apple juice, as the time between '89 and continuing.

And one of the things I know that USDA is doing is

an increased pediatric surveillance, a food consumption study to allow for, I think, eventually like 10,000 children. I think that's been completed. I think the ends in the infant and the one-to-two-year-olds in the CSFII, either '94 to '96, are relatively low, and that additional children were needed, I believe, to increase our knowledge about what children are actually exposed to. I'm wondering if any of that has been taken into consideration.

DR. ZENGER: We didn't have access to that data, to my knowledge. You know, this consumption, '94 to '96, was what--you know, what we have access to and what we typically use. I mean, we could run that analysis again based on other intake data if we had it, but at this point--

DR. SIGMAN-GRANT: I think they're just about finished collecting the data. I don't think it's available --well, it isn't available for public, but I don't know if it would be important or even to look at, just general, this appearance data, to indicate whether there's been an actual maybe increase in total consumption over the years, because --just because of that scare incident.

DR. ZENGER: Well, it would certainly be something we could look at, you know, as part of our--if we do set an action level, that could be something we could take into account in our document that would--

DR. SIGMAN-GRANT: Because I don't know if it

would change exposure, potential exposure rates over a lifetime, but it might.

DR. BENEDICT: All right. Anyone else? Dr. Hotchkiss.

DR. HOTCHKISS: Yes. Dr. Bolger, my thumbnail math is letting me down a little bit here. I'm just trying to quickly push through to get the .43 number. Was that based on the 100 microgram per kilogram per day or per week of Becci?

DR. BOLGER: Yes, it was based on the low dose level.

DR. HOTCHKISS: So then you divide that by seven--

DR. BOLGER: But is it 100 micrograms a week?

DR. HOTCHKISS: It's 100 micrograms per kilogram body weight weekly.

DR. BOLGER: It's three doses, so that would be 300--

DR. HOTCHKISS: Right, right.

DR. BOLGER: --divided by 7--

DR. HOTCHKISS: Yes.

DR. BOLGER: You should get 43.

DR. BENEDICT: Okay, so anyone else? Dr. Applebaum?

DR. APPLEBAUM: If either Dr. Bolger or Dr. Troxell could just very quickly take us through the process

by which the paragraph on page 3 of the letter that was sent to CCFAC in '98 where you talk about the 500-fold safety factor. Starts off with "moreover". It's right after--do you see it?

DR. TROXELL: Yes, yes.

DR. APPLEBAUM: Can you just take us through, because I seem to be having the same type of problem with my pen not being able to add properly, and just to take us through that 500-fold safety factor, because that is--that's significant in terms of the safety provided.

DR. TROXELL: Okay. The PTDI is .43 micrograms per kilogram body weight per day. That is--that incorporates a 100-fold safety factor. If you go to page 4 of Table 2 for the juice samples with a limit of 50 ppb excluded, you will see the 90th percentile all ages consumer is at .078. And if you do your math there, you should get another factor of a five, approximately. I think the factor is 5.5.

DR. APPLEBAUM: Okay.

DR. TROXELL: So 5.5 times 100 gives you 550-fold safety factor when you look at this from the all ages viewpoint.

DR. APPLEBAUM: Thank you.

DR. BENEDICT: Further questions? Dr. Hotchkiss.

DR. HOTCHKISS: I'm sorry, I'm still confused.

Maybe because I haven't studied this, obviously it's because I haven't studied this carefully enough. But the Becci paper doesn't seem to make this 300 very clear to me. I mean, let me quote it.

It says, "Animals received patulin by gastric intubation three times a week at levels of 0.1," and so forth, "milligrams per kilogram body weight." Does that--

DR. BOLGER: You're looking at the paper?

DR. HOTCHKISS: Yes.

DR. BOLGER: Okay. They did that three times a week. Okay? So the total dose, say at the low dose, would be 300 per week.

DR. HOTCHKISS: Per week.

DR. BOLGER: They did it three times per week. Okay. The total dose is 300 micrograms--all right?--at the low dose.

DR. HOTCHKISS: Well, that's not what it reads to me. That's why I'm curious about it, because that's not what it says. I mean, if you're sure that's what it is. It says the dose levels of patulin used were those levels per kilogram body weight, period.

DR. BOLGER: Yes. They only did it three times a week. We did go back and look at this study. As a matter of fact, we pointed out to JECFA, because when they first looked at this study, they--because the paper is a little

unclear, all right? And when they first evaluated the Becci study, I think it was in 1990, they made the same assumption, that it was a daily dose. We pointed out to JECFA that it was not a daily dose, it was three times a week, and pointed out the error in dosage, and in fact that's what they corrected their dose and ended up a .4, so--

DR. HOTCHKISS: So you're confident it was 300 and not as the paper reads?

DR. BOLGER: Well, because we pointed out the error in JECFA's original analysis, so yes. In fact, I went back over it again last week because, you know, every time I go back over it I always wonder, "Did I do this right?" But several of us have looked at that, JECFA looked at it, reached the same conclusion. So it's not a daily dose, it's three times a week.

DR. HOTCHKISS: No, I understand that, but it doesn't say--it just says levels per, it doesn't say when. It says it was given three times, but it doesn't say what the doses were that were given each time. It just says what the dose was.

DR. BOLGER: Well, I--okay.

DR. BENEDICT: Did anyone call Becci and find out?

DR. BOLGER: No.

DR. BENEDICT: In all these deliberations?

DR. BOLGER: I didn't. Let's put it that way. And I have no firsthand knowledge that anybody did. So, I mean, yes, that's something we could do to just double-check on that.

DR. BENEDICT: Additional questions? Dr. Kuzminski?

DR. KUZMINSKI: What is the--I'm not sure who I should direct this question to, but what is the variation in the analysis, the variability around--you've given the sensitivity level or the detection level. What's the variability of that?

DR. BENEDICT: Say your name when you answer.

DR. ZENGER: Dr. Zenger. I'm not sure exactly what you mean by "variability." When you run that iteration and it calculates the probability plot, you get a distribution plot for the results, so there is no real variability around that plot. You get, you know, 200,000 points. They give a point estimate for a consumer, you know, and those are plotted on the probability curve.

DR. KUZMINSKI: The question was directed to just an analysis of samples containing patulin, and I guess what is the coefficient of variation of the analysis?

DR. BENEDICT: Dr. Troxell?

DR. TROXELL: This is Terry Troxell. We don't have our analytical expert here, but certainly when we set

an action level and when we consider enforcement action, we would certainly take into consideration the reliability of that number that the sample actually exceeded 50 ppb. I mean, I think fairly clearly at this point the analysis can go down to 5 ppb, so if it can go down there, with quantification the variation probably is fairly good.

DR. ZENGER: Well, if you're talking about variation around--for an analysis of patulin, okay, that's a different story. That's lab-dependent, and the variability can be fairly high. It just depends on which lab is doing the analysis and how good they are. But all we have for a patulin level is the point estimate. We don't have an estimate of the variability of the patulin level for a sample, for any individual sample.

DR. KUZMINSKI: But given that, and given the comment by Dr. Troxell, the 50 ppb level would include that variability.

DR. BENEDICT: Could you answer verbally, please?

DR. ZENGER: Yes. Dr. Zenger. Yes.

DR. BENEDICT: Dr. Sigman-Grant?

DR. SIGMAN-GRANT: I guess my math is--it must be late in the day or something. I'm looking at the Table 2 where you have the 90th percentile and the exposure is .42 micrograms per kilogram body weight, and you're setting the level at 50 micrograms per kilogram. To me that's only a

10-fold difference. And that's in the apple juice, I recognize that.

DR. ZENGER: I'm not sure exactly what--

DR. SIGMAN-GRANT: Now I'm getting confused. I need to figure out the weight of the juice.

DR. ZENGER: Yes, right. You have to take into account the intake.

DR. SIGMAN-GRANT: The other column. Okay. Right. Sorry.

DR. BENEDICT: No, that's fine. Anyone else?

Well, the Chair will ask just a small question. When the rats died, what was the cause of death? Whoever would like to answer that.

DR. BOLGER: You mean the histopathological diagnosis?

DR. BENEDICT: Anything.

DR. BOLGER: The thinking was that because patulin is an antibiotic and it's selective for Gram-positive, I think it is, that you then select out for Gram-negative and you have a bacterial infestation, I think is the best way to describe it, as one of the primary responses. But remember this has a pronounced effect on sulfhydryl groups, so it affects any number of enzyme systems.

DR. BENEDICT: No, I understood the cell biology and the biochemistry, but you have a dead rat.

DR. BOLGER: Right.

DR. BENEDICT: What killed it?

DR. BOLGER: I'm not sure that--

DR. BENEDICT: Was it respiratory, was it tumor, was it--

DR. BOLGER: Oh, yes. Yes. It was pulmonary edema and respiratory distress.

DR. BENEDICT: Presumably because of the ion problems, that--

DR. BOLGER: You get all these massive disruptions of ion fluxes across cell membranes, you get exudate in the lungs, and they just suffocate on their own fluid.

DR. BENEDICT: Sure. Okay. So was this--when the males lose weight and when the females didn't was this confounded some way by the--you probably can't answer this, didn't do the study--but is it possible that that was not a reaction to the chemical but something to do with the gavage procedure? Do males react more violently to being gavaged than females do? Is there some confounder there that hasn't been looked at? Did they get ripped up more?

DR. BOLGER: Well, my experience has been, I mean, that's always a tricky--gavage is always a tricky technique, but it's not selective to one sex. I've never seen a study with that as--I mean, if it's a problem, it's a problem in both sexes.

DR. BENEDICT: Sure.

DR. BOLGER: So, you know, that's the only thing I could base it on.

DR. BENEDICT: It's a fairly trivial question, I realize that.

DR. BOLGER: Oh, no. No, I mean that could be a real problem. I mean, you could, if it were a particular problem in gavaging one sex over the other, that could be an explanation. Now, the authors didn't note anything like that, so I would have to presume that it was not something that was a problem that was just in one sex versus the other.

DR. BENEDICT: Sure. The last thing I'd like to ask is, with respect to the carcinogenicity question, I notice in the list of organisms that Penicillium roqueforti is a producer of this substance, and it would seem to me that someone could check people that make blue cheese, and first of all, do you find an elevated level in blue cheese? If you don't, that's fine. If you do, do blue cheese workers have some anomaly?

DR. BOLGER: As I pointed out, the problem is nobody has done a study. Now, whether you could do a study, maybe that's a possibility.

DR. BENEDICT: Dr. Buchanan I think is busting to speak.

DR. BUCHANAN: A point of clarification. Patulin is one of a series of polyketide mycotoxins. Those are under very strict control as secondary metabolites, and the substrate cheese, which is low in carbohydrates and high in proteins, do not support the conditions that would lead to any substantial production of patulin in cheese. And in fact, the analysis for the levels of most mycotoxins in cheese turn up consistently very, very low because of that, and it's pretty consistent for all the polyketides.

DR. ZENGER: Dr. Zenger. Yes. I mean, that's been looked at in the literature. If you look at that, patulin has been looked for, and again a lot of this is strain-specific, also, and the particular strains which are low in these kind of production of metabolites. So there are varieties of Roquefort A.I.that do produce high levels of patulin but there are others which produce almost zero, so producers have a tendency to pick those that produce zero.

DR. BENEDICT: Thank you.

Dr. Montville?

DR. MONTVILLE: I'm going to grant your mathematical superiority, but I have I think a philosophical question about at what level FDA is required to protect the health. And that's going back to Table 2 on page 7. The 50 micrograms per kilogram is based on the JECFA permissible

tolerated daily intake of .43 micrograms per kilogram body weight, and the one-to-two-year-old 90 percent intake is .42, which is pushing that, given, one, maybe the question of whether the consumption is adequate; two, the assumption that children need more protection than adults; and, three, we don't know how long the tail is, so in the 99th percentile, would it be over, and how far? I'm just a little uncomfortable with that.

DR. BOLGER: Well, I guess a couple of answers, and that is, when you look at patulin and how we're approaching this, it's really not that inconsistent with how we do these kinds of safety assessments and compare them to these exposure assessments. Bear in mind, these exposure assessments are conservative. Okay? We are overestimating what exposure is. We're taking a two-day survey and extrapolating into chronic intake, and we know from every survey we've ever done this on, if you have a biomarker, okay, where you can do a reality check, we're always over by a factor of three to five. Okay?

I'll take methyl mercury as an example. If I take my methyl mercury exposure assessment and then I compare it to my hair levels, I'm over by a factor of three to five. If I take lead, okay, and I estimate what the exposure would be, taking a two-day survey, using it for chronic exposure, and I compare it to blood lead levels, I'm going to be over

by a factor of three to five.

So, you know, we have some history of experience here of using these kinds of surveys this way for chronic exposures. We don't like it, but that's all we have. We don't have any long term. We used to have 14-day surveys from MRCA. We don't have those anymore. Okay? So we have a number of conservatisms built into it.

Yes, if you look at over the 90th percentile, as you said, you're pushing that safe level, and so you could say it would be 10 percent or over the safe level. But the safe level is just that. It has a margin of safety built into it, too.

I mean, because you go over this bright line, the term that's always used is, you are now at risk. Well, I don't know what that means. That means you're above the safe level, but it doesn't mean that your risk has changed at all. You could go 10-fold above that and your risk doesn't change one bit.

So, I mean, I think because we have these conservative steps built into the analysis like Mitch went over, I don't think that we're that inconsistent with how we look at these kinds of contaminant issues. But your point is well taken, and one we're very mindful of.

Terry, you want to say something?

DR. TROXELL: Yes. Terry Troxell.

I just want to add that the comparisons that Mike was making to lead and mercury are really talking about comparisons of two-day exposures to blood lead changes over a short period of time, or hair changes over a relatively short period of time. We're talking here about looking at a lifetime bioassay and comparing it to two-day results, so the exaggeration is likely to be even greater.

As I was trying to say, the agency, in evaluation of chemical contaminants or additives and so on, looks at the overall process with these substantial safety factors, as well as looking at 90 percentile as being an overall very conservative and robust process that effectively protects all consumers.

DR. BENEDICT: Dr. Hotchkiss?

DR. HOTCHKISS: Before we vote on this, which we're going to do, I just want to point out to the committee the--generally the procedures used here are well accepted in the toxicological community and supported worldwide, in my experience.

DR. BENEDICT: Could you get a little closer?

DR. HOTCHKISS: But the number that--of the permitted tolerable daily intake is based on a single number from this study, which I think is not a problem either, except that when I read this study, it's unclear to me what that number actually is.

I'll point out to you, for example, in the author's study they have one table, they put milligram per kilogram body weight per day, and they put the .1, .5, 1.5 numbers in that table. That's a daily number they put in that table. Now in another table they put milligrams per kilogram body weight with no time factor on it.

In their design of the experiment description, they say the dose levels of patulin used were 0, 0.1, 0.5, and 1.5 milligrams per kilogram body weight, period, no time factor added to that, so you don't know what they mean by that. Later they say "test solutions," not describing what those test solutions were or their concentration, but "test solutions of patulin were administered by gastric intubation three times per week."

So at least as I read this, unless somebody can correct me, it looks a little equivocal to me without further checking into exactly what was given to these animals, and that's the basis of this decision.

DR. BENEDICT: Dr. Bolger would like to reply.

DR. BOLGER: I mean, maybe it's because I've been looking at these for 20 years. I mean, what they described in their design, okay, it's pretty clear to me what they're saying is that they have three dose levels. They're giving a gavage here. This is not a dietary, so they're giving a gavage and they say "We do this three times a week."

So that tells me, okay, that that's the frequency of administration over a week's time span. They didn't say "We did this on a daily basis." We did it three times a week. We used these three dose levels. And that's a fairly standard way of describing it, okay, for a gavage study.

Now the table, I'm not sure what table because I was trying to scramble real fast, looking at what you were saying.

DR. HOTCHKISS: Table 2--

DR. BOLGER: Table 2.

DR. HOTCHKISS: --sex and patulin level.

DR. BOLGER: Yes. Okay, but that's not--and I agree. You're right, that's not what they're saying in the design. Okay?

DR. HOTCHKISS: Well, we can debate what they said in the design, but--

DR. BOLGER: Well, I can't resolve it, yes. I mean, the best way to do it is call someone.

DR. HOTCHKISS: Or the best way, what they should have done and the reviewer should have made them do is say what the concentrations were and the dose levels, or what the daily dose levels were, or how much of a certain concentration was. It could be interpreted, in my view, either way.

DR. BENEDICT: Dr. Russell?

DR. RUSSELL: I think this is more along philosophical lines, too. You think you have a 100-fold safety factor for infants, and I guess the point I want to make is that the infant is not just a smaller version of the adult. You pointed out some differences, but in addition there are huge differences in the gut, particularly with their much more permeable gut and their much more immature immune system in the gut.

So I would want to make sure, I think it harkens back to something that Dr. Sigman-Grant said about making sure that your intake levels in that age group are in fact the most current intake levels that are available, and I would definitely check with USDA to see if they have, and the National Center for Health Statistics to see if they have more up-to-date data on that age group. I know they are over-sampling in that age group, just as they are in the elderly, because in the past we don't have good information on those two age groups.

DR. BENEDICT: Anyone else? Anyone with a comment or a question? Complaint?

[No response.]

DR. BENEDICT: Okay, so this puts us well ahead of schedule. I have to ask the boss for a clarification. We're scheduled for a break at 3:10, and the important number here that I have written down is 3:25 for the public

hearing. Is that flexible? Has anyone else signed up?

MS. DeROEVER: No.

DR. BENEDICT: And if not, has Dr. Matthys--is he prepared to speak if we truncate the thing?

MS. DeROEVER: He's here.

DR. BENEDICT: Okay, so if there are no further questions from the panel, why don't we accelerate and take the break now? We'll come back, have the public hearing, maybe a few more questions will appear to you, occur to you as we're breaking, and then you can have a chance to ask a couple more questions, and then we'll answer the questions from the FDA. So let's come back in 15 minutes, which will be 2:30--I'm sorry, 3 o'clock by my watch. Thank you.

[Recess.]

DR. BENEDICT: We can take just a second while we're assembling to pass this out, and we'll make this available I guess at a later time for the vast crowd behind me. Does everyone have a copy of those handouts that would like to have one, at least around the table? Okay.

Let us resume, and just before the public hearing, I'm going to ask Mr. Alex Liberman, who is the attorney, to make a brief statement. He has a point of clarification that I think is useful to make.

MR. LIBERMAN: I'll be very brief. I just want to remind the members of the Food Advisory Committee that an

action level is merely a form of guidance. An action level is not binding on the courts, the public, on food makers or the agency itself. Action levels do not have the full force and effect of substantive rules or regulations. I just want the committee to keep that in mind, that we are talking about an action level at this point in time.

DR. BENEDICT: Thank you.

Okay, let's enter into the official open public hearing, and we're going to hear from two people. First we'll hear from Dr. Allen Matthys from the National Food Processors Association, and talk among yourselves until he gets his microphone on.

DR. MATTHYS: Good afternoon. I'm Allen Matthys, Vice President of Regulatory Affairs for the National Food Processors Association. NFPA is the principal scientific trade association representing the food industry. With three laboratory centers, NFPA is a leading authority on food science and safety for the food industry. For more than 90 years, the food industry has relied on NFPA for various government and regulatory affairs representation, scientific research, technical services, education, communications, and crisis management.

The issue of patulin in apple juice has been reviewed extensively by our Juice Products Technical Committee. Patulin is produced by various molds that infect

apples, as you have heard today. If moldy apples are used to produce apple juice, patulin is likely to be present in the juice.

The presence of patulin serves as a good indicator of the quality of the fruit used to produce the juice. Patulin levels in excess of 50 ppb in apple juice and single strength apple juice from concentrate are more likely to be associated with excessively moldy fruit. Proper fruit selection, handling, sorting, culling, storage and washing can assure that only good quality fruit are used to make the apple juice. Use of these Good Manufacturing Practices can reasonably assure that the juice will not exceed the 50 microgram per kilogram or part per billion level.

On November 1, 1996, NFPA requested the Food and Drug Administration establish a guideline or action level of 50 micrograms per kilogram as a maximum limit for patulin in apple juice and single strength apple juice from concentrate used as an ingredient in food intended for human consumption. This action was taken on behalf of NFPA's Juice Products Committee.

Many U.S. companies that process and/or purchase apple juice and apple juice concentrate have product specifications establishing a maximum level for patulin of 50 micrograms per kilogram based on single strength juice. The U.S. Food and Drug Administration has not yet

established an action level for apple juice. We would hope that they would be able to do so in the near future.

As mentioned also by Dr. Troxell, this same action level is under review by the Codex Committee on Food Additives and Contaminants, and by the Codex Alimentarius Commission. It is at step five in the process, going before the commission next week, so we hope that will move forward also.

Because the U.S. FDA has no defect action level or guidance limit for patulin in apple juice, NFPA members report rejecting shipments of imported apple concentrate which exceed the 50 microgram per kilogram limit established in their company specifications. They speculate, and likely rightly so, that that product is not re-exported out of the country, but is instead diverted to other companies that have not established an action level for patulin, and therefore that product is on the U.S. market.

NFPA members also report that since they have established action levels, that their product rejection rate has decreased from the area of 10 to 15 percent in around 1995-96 down to about 2 to 5 percent in 1998. That is in part based on the fact that they are selecting suppliers who consistently provide them product that meets or is below the 50 ppb limit, and they know that if it's above it, that product will be rejected.

Also, the 50 microgram per kilogram level would fall within current analytical capabilities. That's a plus or minus 10 micrograms per kilogram, based on discussion with industry chemists; that they feel, when they run a sample, they are probably plus or minus 10 around that limit if they're looking at 50 as their limit.

The current AOCA method, and I've provided you a copy of that, 995.10, was collaboratively studied using levels of 20, 50, 100, and 200 micrograms of patulin per liter of juice. In talking to some of the laboratory people about how they would handle a sample coming in, and this is the practical side: If you receive a sample from a supplier, you routinely test what's coming in to your company, how do you handle that when you get a number?

If that test is over 50, you're going to reject it. With one company, if it's under 30, we'll accept because we know we have enough leeway now that further tests will put us under 50, even though we have a plus or minus 10 at this level. If we're from 30 to 50, we will re-test to better quantify that number. If that second test comes out over 50, we'll reject.

So we're doing two tests because of the variability of the method. That's current practice now, definitely within one company and certainly within others who are looking at that, so you have a plus-minus reject.

So the test, we do not feel at this point, for routine analysis is adequate below 30 to do a real good quantitative without doing multiple tests, and then you have to average those numbers together to figure about where you are. That can get to be a problem if you're dealing with compliance criteria where you've established a number.

So we feel, based on that and based on other evidence we've seen here today, that 50 is an appropriate number and we should move forward with that number as quickly as possible. Thank you.

DR. BENEDICT: Thank you, Dr. Matthys.

We'll have a second speaker, Dr. Andy Ebert of Keller Associates, who will make his way to the podium at this time.

DR. EBERT: Slowly. I apologize.

DR. BENEDICT: No apology necessary. We're well ahead of schedule.

DR. EBERT: Thank you, Chairman. I recall when I served on this committee a few years back, about this time of day I was hoping for two things: information and brevity. I'll attempt to stick with both guidelines.

I am here today representing the Processed Apples Institute, which, as the name implies, is a trade association. It's composed of those companies that process apples into juice and sauce. Although phrases "as American

as apple pie" are pretty well known, the fact of life is--and this is true for a lot of fruits and vegetables that we consume--about half of the product that our members put up comes from U.S. sources, which means about half comes from non-U.S. sources.

The concentrate that we work with comes from a variety of countries in Europe and most recently in the Orient. And even though the guideline that we are talking about today is that, as pointed out by legal counsel, it is extremely important for those of us who are representing companies that do business on an international basis to (a) have a standard that we can live with--we certainly endorse the 50 ppb figure as being workable and scientifically sound--and (b), we have to have harmony with the overseas activities that you heard about today from Dr. Troxell and others.

We, too, as the question came up before, are interested in what's going on in the marketplace. Someone raised the question, were there any detrimental effects on apple juice and sauce consumption following the Alar scare about a decade ago, and the answer is yes. But as fortunately is the case with so many of these products, there is a dip and a rebound that can be tracked through appropriate market research channels.

However, what's going on here and what I did want

to mention, and I'm not particularly happy to talk about this but it is a toxicologic fact of life which might go into the consideration of this group, unfortunately too many of our consumers are now giving fruit products with the assumption that the ultimate consumer, perhaps their child or a member of their family, is in fact ingesting a product that they believe is 100 percent of the named product, but it is not. It might be, shall I sort of glibly say, a snappy alternative.

And one would see in the case of apple products a number of diluted apple products out there that in fact go into the baby bottle, and mama thinks she is giving her youngster 100 percent juice and is not. Obviously, that gives us, if you go through some of the calculations like Dr. Hotchkiss was going through, some good numbers from a toxicologic standpoint. I don't think we can be very happy about it from a nutritional standpoint, however.

From a practical standpoint, then, it does mean as we go forward with the USDA screening programs, that the tier that one looks at, the identified product, is in fact accurately identified and one extrapolates the data and in fact is using USDA data to reflect what's going on in the marketplace. And there's a flux, there's a change in the marketplace in our industry as well as any others.

I think it's fair to say that our organization

continues to work on an international basis, have been for 10 years, worked very closely with Dr. Matthys and his colleagues. We have a number of people that we go out and have a glass of apple juice with upon occasion.

And I couldn't help but notice just on the plane on the way up here, MAFF, Ministry of Agriculture, Fisheries and Foods, has announced their food surveillance program for 1999-2000, and of the some three or four dozen programs, they will continue their program which they began in 1998, survey of apple juice for patulin. It's interesting the twist that they put on it, because I think it's sort of reaching the point of diminishing returns.

The stated goal is to determine the levels of patulin in apple juice. "This project will establish the exposure of the U.K. population to this mycotoxin and confirm whether the downward trend in patulin levels identified by previous surveys is continuing." I think that the data indicates, well, yes, it has been going down, although we better figure it's going to be leveling off.

Thank you, Chairman.

DR. BENEDICT: Thank you, Dr. Ebert.

Okay, so if there are no additional public speakers, we will move to the questions. Since we're a little ahead of schedule, I could ask one more time, does the panel have any questions of our FDA representatives that

might help clarify their opinions?

[No response.]

DR. BENEDICT: Seeing none, we'll enter into the discussion of the questions posed by the FDA to the committee, and we'll note at this time that the two industry representatives, Dr. Applebaum and Dr. Kuzminski, are going to recuse themselves from the actual vote to avoid any possible conflict of interest problems.

Because of that, I'd like to ask them in turn to give us their opinions in advance of our sampling the panel, and so we should start with Dr. Applebaum. You may say anything you wish, and I'm sure you will.

DR. APPLEBAUM: Thank you, Mr. Chairman.

There are just some points that I'd like to reemphasize, and they've been made very clear by the representatives from FDA today, as well as from our own Dr. Matthys, but I'd like to impress upon my colleagues that, again, this is a guidance. At this point in time there is no level out there, no direction available other than what the industry is currently enforcing itself, and doing an excellent job, if I may say so.

We have requested this guidance because it's important for us in terms of maintaining the safety of the product, which is first and foremost in our members' minds, as well as the quality of the product. We have debated,

both internally as well as externally, the level that we had been requesting. We feel very comfortable in it representing a safe level, for the reasons that have been articulated.

With that, I just want to again mention the fact that we are looking at a global marketplace. We feel very comfortable about the safety of what has been established by WHO, the fact that the industry does not, if you will, attempt to meet the 50 ppb; in fact, the industry is below the 50 ppb. But as you know, when you're doing distributions and you're looking at ranges of products, not everything comes in at a certain number, so you have to look at the range of the product or the ingredient that we receive.

So with that, Mr. Chairman, and I appreciate the fact that, you know, the understanding of being so close to this issue, my objectivity would bias considerably my vote on this. So those are my comments.

DR. BENEDICT: Thank you, Dr. Applebaum.

Dr. Kuzminski, would you like to make a comment?

DR. KUZMINSKI: Sure. Thank you for the opportunity to comment.

I think this, it's not a no-brainer, but this is, as far as doing this and keeping a compound that there is enough of a cloud over from a public health point of view to

a level out of the American diet, this action that's being proposed should be done. Unless there is a national standard, a national action level, the compound at higher than that kind of level, the 50 parts, will continue to find its way into the food supply. So that's basically my comment on it.

DR. BENEDICT: Thank you, Dr. Kuzminski.

So now we will ask two questions of the committee. Then we'll do the same thing we did before. I'll ask you for a yes or no sort of answer.

The first question: The committee is being asked if the available scientific data support the establishment of an action level for patulin in apple juice and apple juice containing products. In short, should there be an action level?

I'll start on the other side of the room. Dr. Hotchkiss, yes or no?

DR. HOTCHKISS: Yes.

DR. BENEDICT: Yes. Thank you.

Dr. Sigman-Grant?

DR. SIGMAN-GRANT: Yes.

DR. BENEDICT: Dr. Montville?

DR. MONTVILLE: Yes.

DR. BENEDICT: Dr. Russell?

DR. RUSSELL: Yes.

DR. BENEDICT: Ms. Richardson?

MS. RICHARDSON: Yes.

DR. BENEDICT: Dr. Brackett?

DR. BRACKETT: Yes.

DR. BENEDICT: Thank you.

Second question: If so, based on your scientific knowledge and expertise, and the exposure data presented, would an action level of 50 ppb be sufficient to protect public health?

Dr. Hotchkiss?

DR. HOTCHKISS: Yes.

DR. BENEDICT: Dr. Sigman-Grant?

DR. SIGMAN-GRANT: Yes. Can I qualify that?

DR. BENEDICT: You may qualify it briefly.

DR. SIGMAN-GRANT: I think that the exposure levels for the youngest, for the children, the under one and one-to-two, I think we need more current information in order to establish that level.

DR. BENEDICT: Thank you.

Dr. Montville?

DR. MONTVILLE: Qualified yes, with the same reasoning.

DR. BENEDICT: Thank you.

Dr. Russell?

DR. RUSSELL: Exactly the same, qualified, with

the same reason.

DR. BENEDICT: Ms. Richardson?

MS. RICHARDSON: Yes. My qualifications are different, though. I think we should also look at the elderly, knowing that assisted living and adult day care and nursing homes push apple juice, just like we push it on children, on the elderly. It should be looked at, and also in light of the fact that patulin appears in other fruits and vegetables, I think as we're pushing five a day, that we need to look at if people--and more people are becoming vegetarians--you know, is there a cumulative effect by eating other vegetables and fruits?

DR. BENEDICT: Thank you.

Dr. Brackett?

DR. BRACKETT: Yes.

DR. BENEDICT: So that ends this portion, unless you have a salient comment you would like to enter into the record, that you haven't entered so far.

Seeing none, we'll just tidy up what's going to happen. We will begin tomorrow at 8:30 in the morning with a public hearing, and we're going to have our discussion of the Dietary Supplement Working Group reports. I know you've all read the briefing book. I encourage you to become very familiar with these issues because we're not going to have a lot of presentation. We're going to have a short

introduction and we're going to go right into discussion.

And so with that, I wish you all a pleasant evening, and see you here bright and early, 8:30 tomorrow morning. Thank you.

[Whereupon, at 3:20 p.m., the committee adjourned, to reconvene at 8:30 a.m. on Friday, July 25, 1999.]

- - -

CERTIFICATE

I, **ELIZABETH L. WASSERMAN,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

Elizabeth L. Wasserman

ELIZABETH L. WASSERMAN