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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR FOOD SAFETY AND APPLIED NUTRITION

NATIONAL ADVISORY COMMITTEE

ON

MICROBIOLOGICAL CRITERIA FOR FOODS

VOLUME III

Thursday, September 23, 1999

8:05 a.m.

The Washington Room
The Washington Plaza Hotel
Ten Thomas Circle, N.W.
Washington, D.C. 20005

MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
Washington, D.C. 20002
(202) 546-6666

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P R O C E E D I N G S

INTRODUCTION TO LISTERIA MONOCYTOGENES RISK ASSESSMENT

CHAIRPERSON WACHSMUTH: We're ready. We're just waiting for Dr. Potter to join us. You did a wonderful job yesterday. Thank you. Today we have the Listeria monocytogenes Risk Assessment and we have changed the presenters and the schedule slightly. If you want to make some notes on this, the introduction will be by Dr. Wes Long. Then we will have an additional presenter under Exposure Assessment and that will be Clark Carrington.

Then in the afternoon after lunch, we will also add Clark as a presenter under Hazard Assessment. We will have the concluding comments after the committee discussion and those will be by Dr. Richard Whiting and then lastly we'll have the public comment. So we switched a couple of things there.

Okay. I think it's time to get started unless there's any business at the head table. Okay. Wes.

DR. LONG: Good morning. On behalf of the Risk Assessment Team, I'd like to thank the committee for inviting us back here again today to present a progress report for you on our Listeria monocytogenes risk assessment.

Just to review, the purpose of this risk assessment, as was described in our Federal Register notice back in May of this last year, is to determine the prevalence and extent of consumer exposure to foodborne Listeria monocytogenes and to assess the resulting public health impact of that exposure, and I might add that that's within the confines of the available scientific data and information.

The result of this risk assessment will be used by the Food and Drug Administration and the USDA to help them reevaluate the current policies. And, of course, again, I say if you know me, you know that I'm going to show this slide. I just want to draw attention primarily I guess not to the committee but to the audience that risk assessment is really just one component of the risk analysis triad, if you will, and that what we're focused on today is the risk assessment and that risk assessment is primarily the organization of the scientific information to provide information to risk managers.

So, again, the risk assessment be used. The scientific information presented today will be utilized by the agencies as one component of their assessment of the current policies and programs with regards to Listeria.

So again, the goals of the risk assessment are to try to quantify the relationship between the consumption of the Listeria in foods and the probability of becoming ill. But the risk assessment is really not focused on answering questions like what is the appropriate level of public health protection or what level of Listeria should be allowed in or on foods? Both of those are risk management issues that have to be addressed and are quite multifactorial.

It also doesn't address what control measures should be recommended for various stages of the food chain. However, there are a number of possible follow-up activities to this baseline risk assessment which may include looking at specific products and analyzing their pathways and the risk of contamination. We may look at the effects of various interventions on the pathogen load and the probability of illness and one of the things that most certainly will happen is that this exercise will help us focus in on what our critical data gaps are.

Just a reminder that this risk assessment is one of many activities that are being undertaken by USDA, FDA and CDC in our attack on Listeria. FSIS has a survey underway to get a better handle on the level of Listeria in ready-to-eat meat products. Both USDA and the Center for

Food Safety are doing a significant amount of research on Listeria monocytogenes in a number of areas. FDA has a grant that is just finishing up its first year to look at dose-response relationships for Listeria.

The Center for Disease Control has FoodNet, which is trying to get a handle on the extent and prevalence of Listeria. PulseNet helps us identify better the vehicles that cause the contamination and they also have a case control study underway which helps us better understand why one person gets sick but another doesn't.

And finally, of course, we have this risk assessment. So this risk assessment is really a part of a unified approach to addressing the issue of Listeriosis.

Okay. We went to Chicago in May. The committee invited the Risk Assessment Team to Chicago and we essentially presented a day-long presentation which was primarily, I'd say, a literature review. We looked at the breadth of the literature related to Listeria and we tried to categorize that literature and the data available in that literature to try to focus in on what data might be useful for risk assessment.

So we posed two questions to the committee. The first was have we located all the relevant data? Do we have all of the information that's out there that might be

useful? And secondly, is our proposed scientific approach sound? So when we went in May to Chicago, these were the specific focal points that we asked NACMCF and the public audience to address.

Since that time, the public comment period has closed. It closed in July. We have been working--our Risk Assessment Team has been working to pursue the leads that we got from NACMCF and the public, whether that be data that was submitted to the docket or conversations from a number of trade associations and other groups. So we worked hard to try to incorporate all of the information we could get into this risk assessment.

And then our team went about doing a really critical data review to identify the key data that would be usable for the risk assessment. Finally, several months ago we started having interactive discussions with our risk assessment modeler and that helped us better define what that key usable data is and we continued to have those discussions with the modeler.

Okay. So today, September 23, we're coming back to you with a critical review of what we consider to be the key data to use in the risk assessment, and when I say key data, I want to talk about both the data that we think will be useful for quantitative risk assessment as well as

perhaps some data which may be well known, either anecdotally or in the literature, which might be thought to be applicable but that we were not able to utilize and we'll get into various reasons why.

We're also going to present our conclusions on the usability of the key data and our assumptions and limitations of that data, and I'll come back to that in a minute. And then we're going to take a preliminary look at the form of the models that are shaping up now that will characterize the risk of Listeria.

So what would we like to get from NACMCF and the public today? I think that we certainly don't want to limit the extent of comment from the audience. I want to remind particularly the public that we're focused on the risk assessment and the scientific data and information. We're going to be asking you some fairly specific questions, but we don't want to stifle your opinions and other information that you might be able to provide that perhaps aren't focused on what we think our key areas are.

And we'd like you to critique our conclusions and our key assumptions. And we're going to try to lay out these presentations so that we very clearly state our assumptions and we're going to try to elicit comments from

you on pretty much each of those assumptions that we've made.

Well, where we will go from here? After we look at the input that we get today, we'll consider it and we'll start then to revise our models appropriately and our data sets that go into those models appropriately and we will perform the simulations. From there, we'll draft a risk characterization report. So the format of today's full day is that in the morning, we'll be looking at the exposure assessment. That starts off with Dr. Hitchins looking at the contamination of foods, and followed by Dr. Bender who will be looking at food consumption data, and then Dr. Carrington, our modeler, will initially be presenting sort of a primer on what modeling is and what data--good modeling practices, I guess, is the term. He'll talk a little bit about good modeling practices, and then he will give you some examples of how he is using the data to develop--model the exposure.

In the afternoon, we'll switch to hazard characterization, beginning with some hazard assessments, definitions and a description of the disease, and what the epidemiological record shows, and that's Dr. Pat McCarthy, and then that will be followed by Dr. Raybourne, who will look at the dose-response approach. Modeling will then

again pick up and review the afternoon's data and information and describe how we plan to model that information.

Okay. So I just want to let the audience know, because I don't know how many people are here for the first time to hear about Listeria, but last time in May when we were in Chicago, we tried very hard to be comprehensive and give a great deal of information about Listeria to set the stage for this risk assessment activity. And we're not really doing that today. Today we're focusing in on the key critical issues and we're expecting the committee, of course, who was at the last meeting, to have retained that knowledge that, of course, most of them already had in terms of background, those sorts of things.

But just very briefly, I will show you the difference between the morning and the afternoon and what's going to happen. This is the exposure model. It starts off with some sort of contamination event and then it looks how the Listeria grows in terms of storage factors, storage temperature, storage time and perhaps practices in preparation like cooking, and that gives you a level of Listeria on a food. It's necessary to have food consumption data to merge with that so that we can get an idea of the level of Listeria consumed per meal.

In the afternoon we're looking at the human response and there are three primary factors that go into that: the food matrix, the difference in strain virulence, and host susceptibility factors. And this has all got to be related from primarily animal data to humans.

And then our modeler, Clark Carrington, puts these two pieces together to develop models that characterize the risk. So that's really all I'm going to say about an overview of what's going on. We're going to get into the detailed presentations now with Dr. Hitchins who's going to talk about food contamination. Tony.

EXPOSURE ASSESSMENT

DR. HITCHINS: Thank you, Wes. Good morning, everybody. As Wes said, we're going to talk about the food contamination module, which is the first module in the whole process. I'd like first to acknowledge my associates in collecting the data for this, Mary-Lynn Datoc, Eric Ebel, myself, Pauline Lerner and Wayne Schlosser from USDA and FDA variously.

I'd like to briefly review the role. Of course, it's to collect quantitative and qualitative data on Listeria monocytogenes food contamination. We then hand this on to our dietary colleagues where it gets harmonized with the food intake data. Then that harmonized data is

used to determine food exposure after perhaps some corrections which we'll get into later. And then the exposure is related to dose-response studies which we'll hear about this afternoon. And finally, the end-product is hopefully estimates of risks of foodborne Listeriosis.

Today then I'm going to talk about the food contamination data collection, what kinds of data and how much data we got, talk about the quantitative and qualitative data availability. Of course, we're most interested in the quantitative data. That is the numbers of Listeria in a food or per gram of food, the concentration, and how those various concentrations that are observed are distributed in some kind of frequency distribution.

We're also going to mention a little bit the shelf life and storage aspects when one counts Listeria in a food. At the time one counts it, one gets a certain answer, but one has to recognize that that's only a sample of the lot of the food and that the consumer may get it before we've counted it or after we've counted it, and that the numbers we count may be different for the consumer. That includes, of course, or this process includes the refrigeration variable, what the temperatures of the storage temperatures are, et cetera.

As a check on this, we've looked at and collected some data on growth of Listeria in refrigerated foods or the behavior of Listeria in refrigerated foods, whether it grows, declines, or stays stable. And that will be a model check, a check of the shelf life storage model modeling part of the analysis.

And finally, we'll consider briefly but very importantly the problem of food contamination density frequency gaps. We don't always have data for particular foods or particular groups of foods. I went over this in May with the committee, but I'll briefly go over it again. The collection sources are basically scientific publications, but we do have some other documented data, particularly from the regulatory agencies. The chronology of the data is that it falls between about 1975 and this year, but I think it's fair to say it mainly falls between 1986 and 1996.

The data we've collected was from studies that were conducted worldwide on all continents except Antarctica, but I think it's fair again to say that most of it is from North America and Europe, particularly Western Europe. So it's basically the bulk of it is from the industrialized countries. We're looking mainly, of course,

at Listeria monocytogenes, but we're not ignoring other data for the genus Listeria, the other species of Listeria.

Interestingly, the bulk of data is for Listeria monocytogenes when one looks at the enumeration data, though there is some Listeria genus enumeration data. We're not really at this time looking at the monocytogenes subtype data, the serotypes and other types of classifications for monocytogenes strains, but we may, of course, later on, if we wish be able to put in some corrections to the exposure when data is available or when we can construct reasonable surrogate data.

The data per se is that there are a numbers per gram types of data and presence and absence type of data. The numbers per gram data is usually, of course, associated with the presence and absence study. One looks at a series of samples to see if Listeria is present and then one counts the Listeria in the positive samples.

In general, the sample sizes are 25 grams and so our limit of detection is about one per 25 grams or .04 cells per gram.

The emphasis is on ready-to-eat foods, that is foods that are not further processed after purchasing. In general, we're not considering raw food, though we've collected a lot of data on raw food. We are considering raw

food in relation to undercooking. For instance, in the case of hamburgers, we don't really have any data for the hamburger on the bun that the consumer gets. So we'd have to correct from raw food data for ground beef or other meats to make hamburgers and correct for the undercooking.

We're not really looking at things, other kinds of foods like reused leftovers or foods that are cooked just before, well cooked just before eating. The next series of slides then gives the numbers of samples that were examined for the various types of data, the quantitative and the qualitative. And the format of the slides is all like this. There's the food and perhaps the specific type of the food, the number of samples examined, the number in which or the percentage in which Listeria monocytogenes is present out of that number of samples, and also the number of samples within this total number that gives us some density frequency data. And this is generally what we're passing on to the dietary team and the modeling group.

I've mentioned already that this is what a positive sample is. So overall, without doing any weighting, taking raw and RTE food data together, there's around 133,000 samples in the pooled data collection. And in these, monocytogenes occurs at about 14 percent, and of

this 133,000, about let's say less, about 20 percent is density data.

Coming then more specifically and breaking it down, we have the dairy food categories, various kinds of cheeses, ice cream, raw milk, heated milks and miscellaneous dairy products such as fermented dairy products and butter and cream, et cetera.

Cheese of this type, the ovine cheese and caprine cheese, goats and cheese, we have a fair amount of data and the presence value is 3.9 percent of Listeria monocytogenes, and in this case most of the data involves density or concentration measurements.

Moving on to soft cheeses, the soft cheeses, we're counting as soft cheeses semi-soft cheeses, and mold-ripened cheeses. We have about 6,000 there and 3.7 percent presence, and a third of those are concentration data.

Other cheese include the hard cheeses and cheese data where we can't really say what kind of cheeses were looked at, quite frankly. The literature doesn't always break these things down. And we haven't had time to write to the authors and ask them if they can tell us what they mean by cheeses.

But we have obviously a lot of those and as one might expect in the hard cheese if hard cheese is a fair

proportion of these, the Listeria presence rate goes down. And we have a fair number of density data on that. Ice cream data, we don't have any density data. Raw milks, compared with heated milks, the Listeria monocytogenes frequency is higher. This rate perhaps is rather higher than I would expect for pasteurized or heat treated milks. It's based mainly on studies in England in the early '80s, and in the milk categories, also we don't really have a lot of density data.

Miscellaneous dairy products, again, rather a low incidence of monocytogenes and a fair proportion of the 2,000 odd data involved density data. I should say at this point that when we pass on the density data to the dietary and modeling teams, that's our interpretation of what quantitative means. Just because we hand on that data, it may not always be usable and I think that will come out as the other speakers present their material.

Ready-to-eat raw pro juice, I probably should put this together with salad materials. Dr. Bender will be talking about how the data that we hand on to them is recategorized to the kinds of data we give them and what they can do with the data. The dietary data is a very finely resolved list of things, much more high resolution

data than ours. Our food types tend to be lumped together and composite.

Vegetables, then, the aerial ones, the ones in contact with the soil or nearer the soil, and then the miscellaneous categories, which are things that we probably can't put into these. We have subterranean. As one might expect near the soil, one might have a higher frequency of monocytogenes contamination. Again, we don't really have a lot of density data. I'm not sure all of this was usable in any case, but we hand it on just in case.

This usability of the density data might become clearer when I show you some of it towards the end of the talk as an example. Fruits, proximal, fruits proximal to the soil, we don't really have any data at all. Distal to the soil we have a little bit of data. This value is rather high and I haven't had time to go into that and explain why it's rather high, but in this category there are quite a lot of fruit, dried fruits and nuts and things like that that may be responsible for this being higher compared to things, other kinds of fruits that contain more moisture.

Salads, basically there were three types of salads, at least in the beginning of our categorizations: vegetable--well, non-meat, and then meat, fish and egg

salads, and the things that didn't fall into these categories.

Not too much data on this here. I think Mary Bender will be telling us a little bit about how they dealt with this data and the ready-to-eat vegetables. And the presences are between five and nine and we have a little more quantitative data here. A fair proportion of the available data is quantitative for the meat, fish and egg salads and a fair amount of quantitative data here.

Cooked meat categories, beef, pork and lamb. Pork and lamb, we really don't have any data in this category, very little, and of course, this is--I put a question by this, because it's obviously based on a small sample. So poultry, very little quantitative data and beef, cooked beef, very little quantitative data. And the raw ground meat category as opposed to just plain raw meat, carcass type meat presumably, again we're lacking quite a lot of a quantitative data in the various groups, and as expected, at least beef and pork are rather high in terms of presence data, though we don't really have too much data. And lamb, we don't have any data to speak of. It goes along with the fact that I think in this country very little lamb is consumed.

The raw meat categories, again, in general, we don't have a lot of density data. Pork, we did quite well really. We've got some density data there and the incidences of monocytogenes in raw beef and pork are relatively lower compared--if you remember, the ground varieties of these meats were much higher, several fold higher.

Other meats and products, the deli luncheon type meats, fairly high occurrence of monocytogenes and a fair amount of quantitative data, not high in proportion to the total samples examined, but some there. Sausages, not much quantitative data. Beef jerky, a lot rate of Listeria contamination, as one might expect, and no quantitative data. The exotic meats and products are mainly the pates which are consumed mainly in Europe and have quite a high--at least during the periods in which they were examined had high rates of incidence and some quantity of data. And I put in eggs and egg products here, very little quantitative data there.

Sandwiches, two types, the burgers and the deli sandwiches. No data on the burgers, as we mentioned already. The deli sandwiches, we have a fair amount of quantitative data, high proportion of the samples examined yielded quantitative data for sandwiches, a fairly high rate

of mono contamination. Again, I think most of these sandwich data were from Western Europe.

Ready-to-eat seafoods, fin fish, shellfish, smoked seafood, and then miscellaneous which is data that just says "seafood" so we don't really know where to put it so it's down here. Again, fairly high rates of contamination although shellfish is rather low. And density data quite good for fin fish, a fair proportion of the samples examined there density or concentration data. Smoked seafood, the density data is reasonably good. Shellfish is some density data. The raw seafood categories, fin fish, shellfish, and miscellaneous, what we can put into fin fish and shellfish, rather low, no density data here, and not too much density data for raw seafood. This is really not a thing that we're too interested in obviously from the point of view of ready-to-eat foods.

Other food categories that we had in the beginning were these things here and I think it's fair to say we have no density data at all for these. We have a lot of other contamination data which I've categorized as various, fairly good amount of density data for it. This includes all sorts of things. Infant foods, dietary foods, oriental dishes, whole miscellaneous collection of foods. Oh, and most important, the most important one is the bakery category.

Not really using this in this study. Not planning to anyway.

What's the data look like in terms of numbers? I sort of pulled together some soft cheese contamination density frequency distribution data, and we have the density or number per gram and then the number of samples that fall into that at that density or number per gram or at least the range of density. So in the total range that was covered in these studies, there were 2,000 odd samples, and most of them were below the limit of detection. 2000 odd had no detectible Listeria.

And then in the next category up, 62 out of the 2,000 odd. Less than 100, 16. Less than 500, 49. 100 to 1000, one. 500 to 1000, one. And continued. 1,000 to 10,000, eight. 100 to 10,000, zero. 10,000 to 100,000, four. Greater than 1,000, 13. Greater than 100,000, one.

The categories obviously are not as smooth sort of line of categories, as you can see. They jump about and they're done in different ways. This is partly because there's three studies involved in this pool from two countries and apart from the ways in which they enumerate the Listeria, they choose to present their data in various ways. So it leads to these rather, sometimes rather not matching types of food categories. So this gives you some

idea of the data that we're getting out of the data collection and passing on to Dr. Bender and our colleagues and to the modeler.

A problem that I've mentioned before is that when one counts the food, that count you get may not be the actual count that the consumer gets in his particular sample from that lot of food because he may have sampled it earlier than you or he may have--he or she may have eaten it after you sampled it some time. And so this differential between the analysis and ingestion times may affect the actual, you know, the estimate of the count. And this will be less critical when there is a short shelf life and perhaps more critical when there's a longer shelf life.

And so what Dick has done is used the pathogen modeling program to model growth in products. I'm not going to be showing you that data per se, but I'll talk a little bit about it. So he's using the USDA pathogen growth modeling program and looking at the various parameters of the food that affect growth such as temperature, pH, salt, and nitrite levels and things like that, and, of course, in regard to temperature, particularly we're interested in refrigerator temperature distribution, and we have some figures on that from both Europe and the USDA.

So we'll be able to model what's going on in the food to allow for how the particular estimate of the count may alter for the consumer. As a sort of check on the modeling, no model is perfect. We're also collecting some literature data on growth and persistence of Listeria in foods and then from that we made some calculations of the times for one log number increase or a times ten increase.

And here's a selection of that data. There's a lot of it. It doesn't cover all foods anyway, but I haven't given to you all anyway. For instance, in pasteurized milks or milks heated in various ways, the time for a tenfold increase in numbers at refrigeration temperatures, and these refrigeration temperatures vary in the various studies that make up the individual food categories, three to seven days, for instance.

Deli luncheon meats, five to seven. Poultry cooked, one to five. A lots going to depend in these numbers on what the kind of atmosphere the food is stored in if it's a meat type product. And so we have some other numbers that give us, you know, at least a check on what the model comes up with. These may confuse you. Basically in these cheeses the numbers are going down so in order to increase, you have to go minus days, and they're going down slowly.

Now, in the soft cheeses, initially during manufacture and ripening, any contaminating mono and Listeria may go up, but from the time the cheese is marketed, there's generally a down trend. And obviously there's a lot of variability in these numbers. So anyway we have, you know, a whole slew of these numbers to act as a check on the modeling.

The next to the last thing I want to do before summary, the thing I want to do before summarizing is to look at some possible considerations for surrogates for data gaps. If we don't have any monocytogenes enumeration data, we could use enumeration data for Listeria for that food if it's available. That would involve having to say something like 30 or 40 percent of the Listeria species enumerated are monocytogenes which would be a fair statement. So we could do that. As I already mentioned, the Listeria monocytogenes data, enumerated--sorry--the Listeria enumerated data is actually in the minority relative to the Listeria enumerated data.

Or we could use monocytogenes data frequency distribution data from related food types, again, taking into account the pHs and temperatures, et cetera, of the surrogate food type, making sure they sort of match up reasonably well. The other thing we could do is use

presence and absence data if that's the only thing that's available. That might be a possibility to do that. That would require certain assumptions about the form of the distribution of the data and the things like standard deviations or whatever the particular parameter for the type of distribution that is used and our modeler uses obviously several types of distributions, not just the log normal distribution.

So I should say also that we haven't in the case where there's enumerative data at this time passed on the corresponding data for that food which is incidence data. We should pass that on because what it does is it strengthens the lower end of the distribution curve a little bit.

So to review what we've talked about and where our module fits in, we've done the contamination data. This is going to be interactive with the consumption data to give some kind of exposure estimate. This may be corrected in various ways, for instance, by shelf-life growth modeling, and we also may correct it or complete it, if you like, by using surrogate data. And then once we have our final exposure data, this would be correlated to see what kind of function it is or what kind of listeriosis risk it will give us.

So in regard to--finally, in regard to the contamination data, I think we would all welcome any further suggestions for improving the contamination module. Thank you.

CHAIRPERSON WACHSMUTH: What we would like to do now is to have just a few questions for clarification.

DR. WHITING: Okay. This is Richard Whiting. Just a quick clarification question. You had the numbers of studies, but then you had density. Was that actual individual numbers of data points? Is that what you meant by density so one study could conceivably contribute 25 or more data points to it? You had something like, you know, you had like 1,000 studies, two percent were positive, but then you had 1,000 data points. Could you just explain that a little more clearly?

DR. HITCHINS: Yes. Getting all this stuff on the slide is often hard to choose a word that will be appropriate and yet be meaningful. I didn't want to put cfu per gram, although I think 99.9 percent of the audience would be aware what I meant, but basically with any food type, there's a number of samples that was examined for presence and absence and/or enumeration. Out of that number of samples is a certain number that were enumerated and that would be the number in the density column. Does that answer

your question? And each of those numbers is a pooled number from various studies from various laboratories in various places.

CHAIRPERSON WACHSMUTH: Dick, is that--

DR. HITCHINS: It's not the density. The number in the density column is not a density per gram. What I'm trying to show you here, and perhaps I belabored it and not make it clear enough, is that we have a lot of presence and absence data, but we don't have a lot of enumeration data.

CHAIRPERSON WACHSMUTH: Thank you.

DR. HITCHINS: In most cases.

CHAIRPERSON WACHSMUTH: We have another clarification question. Peggy, Dr. Neill.

DR. NEILL: Hi. I'm wondering on the slide, I'm not quite enough to have figured this out, you had the time to tenfold increase was expressed as days, and it had a number of food types. Yes. Could you explain the numbers for cheese?

DR. HITCHINS: Yes, I probably shouldn't have done this. Then I wouldn't have to answer your question.

[Laughter.]

DR. HITCHINS: Basically what's happening in these cheeses is that numbers when one does spiking experiments with cheeses, the initial number goes down rather slowly.

So you don't get an increase. So in order to get an increase, you have to go back in time. Okay. So if I have a number at time zero when you counted, you can say that 100 days before that, it would be one log higher. It probably be unreasonable anyway to go back 100 days at the time you count it, but this is what the data says. If it makes it easier for you, just say no growth. Okay.

CHAIRPERSON WACHSMUTH: And this is also modeling. These are not actual data points.

DR. HITCHINS: No, these are from the literature.

CHAIRPERSON WACHSMUTH: Oh, this is from the literature.

DR. HITCHINS: Yeah.

CHAIRPERSON WACHSMUTH: Sorry. I apologize. Cathy.

DR. DONNELLY: Dick, I had a question and I may have misunderstood, but what I thought I heard was in the overall risk assessment, you're going to concentrate on ready-to-eat foods and not on raw food products. Is that correct?

DR. LONG: Yeah. Tony is looking--maybe I'll answer it. It is, but keep in mind that the next step is Dr. Bender and she's going to look at consumption. So we don't eat a lot of raw products. All right. So we're

finding these levels. But we do eat some. She's going to match that up.

DR. DONNELLY: Yeah, well, that's what I wanted to question because I think if you look at the epidemiological data that's come out from the CDC, undercooked food products show up frequently as sources of contamination. Products like sushi wouldn't be part of your overall data. So I'd like to put in an appeal to look broadly at raw as well as ready to eat foods.

DR. HITCHINS: We do have data on sushi. It's tucked in there somewhere. I think it's possibly under the raw.

CHAIRPERSON WACHSMUTH: Okay. Mel.

MR. EKLUND: Yes. Mel Eklund. What temperature range, refrigerator temperature range are you looking at in this study?

DR. HITCHINS: Well, I mean we're assuming something like the--sorry?

MR. EKLUND: Some of them may be at 50 degrees Fahrenheit and others may be at a lower temperature like 38 or something like that. So it's quite a difference.

DR. HITCHINS: Yes. As I said, we have temperature distribution data that's being published from Europe and from the U.S. Is that correct, Dick? And it's a

distribution and it's something like I think in the centigrade--I'm sorry--one to ten degrees centigrade, I think is the total range, yeah.

CHAIRPERSON WACHSMUTH: Okay. I think we need to go on to the next speaker and we'll have a general discussion of all of these morning presentations following a quick break. Okay. Next is Dr. Mary Bender.

DR. BENDER: I'm going to give you an update on the food consumption module. My name and number are up there if you need to contact me. First and foremost I'd like to recognize some of the members of the Food Consumption Team. Some are here today. We are in the Office of Food Labeling of CFSAN at FDA, and Eric Hanson, Nancie McCabe and Lori LeGault I know are here. We also have Kathy Smith and Susan Brecher. And the people make this module possible, and some of them think we might be done, but we're not. I just want to remind you we do have more work. I find out everyday.

Next, please. Okay. The purpose of this module is to model the consumption of foods that have a high potential for contamination by Listeria monocytogenes. Next, please. In the May meeting, I put forth some questions and gave some tentative answers and I'd like to

revisit those questions and some quickly pass through and some include some of the assumptions that we have made.

A number of the assumptions are in concrete and others are still evolving just like the risk assessment process. Okay. The first question: what are the foods at greatest risk for contamination by Listeria monocytogenes? Okay. Our first assumption states that after a comprehensive literature review, we've selected foods for the risk assessment that have been linked to listeriosis, analytical testing of Listeria, or recalls, primarily from the U.S. or Canadian governments.

Second question: What food categories will best allow the merger between food contamination and food consumption data? And there is not a one-to-one correspondence in a number of the foods.

Assumption two follows: Currently our exposure estimates include only foods with justifiable contamination and consumption level data. Assumption three says that we have selected foods that are primarily ready to eat. Some may be eaten raw or may receive some processing. Others may have been cooked with the kill step, but allowed to cool after cooking, thereby increasing the risk of contamination.

Our food categories are still evolving. The next three slides will lay out the categories that we started. I

don't want to say started with, but the ones that we came to formulate and presented earlier, and then I'll show you where we are today and then our data gaps.

For seafood, we have categories for raw, smoked and ready to eat fish and shellfish. This is where we started. For dairy, we have cheese broken down into soft and then others that we weren't sure what to do with. Ice cream and frozen dairy, fluid milk, miscellaneous dairy like butter or whipping cream, pastries--I'm still in denial about that one.

Okay. The second slide here under this is produce. We do have listed vegetables and fruits, above, below ground, miscellaneous, juices, fruit, vegetables, pasteurized and not pasteurized, and I know that we do have data showing that less than two percent of the juices are not pasteurized. I'm not sure if there's a more current estimate, but that's what we had in May.

We have several salads, sandwiches and subs. Miscellaneous mixed dishes like the Mexican style dishes. Miscellaneous categories, salad dressing. I know there was a recall of blue cheese salad dressing at some point. Egg products and the meat slides. Various categories of beef, pork, lamb and poultry and I know Tony went through some of these. Deli luncheon meats, several kinds. The

miscellaneous bulk link sausages like breakfast sausages. Jerky and dried meats and then exotic meats including the spreads, pate and loaves.

Okay. When I first made this slide, I put final food categories. Not quite. For seafood, we feel that we have justifiable contamination and consumption data for three categories of fish. The ready-to-eat--now this does not include fish sticks. It's dried, marinated and pickled. Ceviche would fall under here. Raw fish where the sushi comes under that. And then the smoked fish.

For shellfish, we have cooked, ready-to-eat, which is the peel and eat shrimp and steamed crab which we'll throw in this next assumption, that peel and eat shrimp, steamed and boiled shrimp and steamed crab may be eaten chilled after cooking, which is a kill step, thus allowing for possible contamination. And we have selected those foods to represent cooked, ready to eat shellfish.

There isn't any place in the consumption data that will say these foods were not eaten hot so we're trying to account for that and to make this assumption.

For dairy, we feel pretty good about our data for soft and semi-soft mold ripened cheese, pretty precise there, Brie, Camembert and blue, and then we have another category for goat and feta cheese. We started out wanting

to have wanting to have a category for soft, but if you have soft, then you throw in cream, cottage cheese, ricotta and we just don't have adequate data.

But those categories are still pending. The soft ripened and the hard cheese, we're just not sure that the data are adequate. This is one important group that should be included, ice cream and frozen dairy, and we are thrilled to have received some data from the International Dairy Foods Association, but it is presence/absence data, so we're not sure exactly how to incorporate this important class.

For produce, the next two slides include raw vegetables and raw vegetables as salad ingredients. So we have taken the salads, the raw vegetable salads, and pulled the vegetables out, and I explain that a little bit later. But these are the foods for which we have justifiable data and this one also, including the lettuce.

As you may know or some of you may know, sprouts is not included here. We don't have justifiable contamination data yet. We'd like to include sprouts and a few others.

Assumption five: The produce data do not include vegetables that have been cooked and chilled before eating. All vegetables were consumed raw except for frozen peas in a layered salad, and I'll talk about recipes later.

We have a category for cooked ready-to-eat meats including consumption of beef, pork, chicken and turkey.

Assumption six states that cooked beef, pork, including ham--it's a biggie--chicken and turkey may be eaten chilled after cooking with a kill step,thus allowing for possible contamination. We have selected those foods to represent cooked, ready-to-eat meats. As with the seafood, we have no way of telling whether somebody has gone on a picnic and taken fried chicken that has cooled or some of the other meats, but we're working with this assumption at this point. Another category for meats: burgers and ground beef patties.

Assumption seven states we will model the exposure of Listeria in raw ground beef by estimating the consumption of ground beef that is not fully cooked in burgers and ground beef patties. We do not have contamination level data for the cooked burgers but for the raw, yes.

Another category of meats: we have hot dogs and bologna under deli luncheon meats and dry and semi-dry fermented sausages like pepperoni and salami. We do not have adequate contamination data for the luncheon meats like chicken or turkey or beef, and then we have included egg/meat/egg salads, but thus far have dropped off the fish till we get more data hopefully.

Okay. Quickly, two slides. If you could please look to see, these are the foods or the food categories for which we do not have adequate data. Some of the cheeses are still up there with a question mark and the ice cream, and we are questioning our data for raw milk, but we do know, of course, that a proportion of the milk consumed is raw, and I know one survey said something it was like less than two percent of the people--it was a CDC survey--stated that they drank raw milk. So there is an issue here.

Okay. Again, the salads--there are some salads remaining. The sandwiches and subs--remember they are pretty much--we've taken the meat off of them so they're not completely at a loss up there, and then we have these meat categories left. And we have no consumption data for raw beef. Maybe one or two eatings of raw beef, but nothing of pork, hopefully not, or lamb or ground poultry.

There were maybe--there were just a couple eatings of pate, but not enough that we would even want to include the consumption. So that's--not sure what to do with that.

Okay. Assumption eight: we assume that if new contamination data are made available to us, we will include additional foods in the risk assessment.

This slide is not supposed to be tacky, but it's--I don't have neon lights or music in the background, but

this reiterates what Tony mentioned. How do we account for the other foods that have been identified with Lm contamination through listeriosis or through analytical testing or foods that have been recalled? Do we use surrogate quantitative contamination level data and bring in those foods which we currently do not have data? Which surrogate data do we use? And I know Tony mentioned several and we really would like your help on this one.

Third question: what are the best sources of food consumption data?

Assumption nine: we're using the best U.S. food consumption data that are available. We went through this in May but quickly there are two major nationwide U.S. food consumption surveys, CSFII, conducted by U.S. Department of Agriculture, and NHANES III is the latest conducted by U.S. Department of Health and Human Services.

The CSFII is the most current survey. There are two 24 hour recalls. It's a nationwide probability sample. The survey provides weights to reflect the population. There are over 16,000 respondents. There's a breakdown up there of groups. The sample for pregnant and lactating is small, too small really for generalization. They oversample the young, the old, low income.

NHANES III is a little bit older. Both of these surveys are working toward merging over the last--well, the latest time period, CSFII, the one just before this, has been collecting data on children for EPA and they should have those data available to the public early in 2000 hopefully. But in 2000, these two surveys plan to use the same survey design and we'll be able to really merge the data and get a lot more respondents.

NHANES III had one 24-hour recall of foods eaten. It's a national probability sample. Weights allow everyone to really reflect the U.S. population. Over 30,000 respondents and there's a breakdown, and they did oversample the young, the old, black Americans, hispanic Americans.

Okay. The next question: which of the over 7,000 food codes do we include? This is an example of what the food codes look like. Lots and lots of food codes. You don't just put in cheese. You have to go through and really be specific. Bringing about assumption two and adding 2a, that while currently our exposure estimates include only foods with justifiable contamination and consumption level data, we have thus far selected food codes to match the foods for which we have contamination level data.

Next question: what measure of food consumption will best represent exposure to Listeria? Assumption ten is

the best measures of food consumption to measure exposure include, first of all, amount eaten per eating occasion in grams. This is a serving a meal.

Secondly, amount eaten per person per day in grams. We have provided data, both types of data, to the modeler and with the second type of data you can calculate percent of population eating or per capita. But remember it's just for those food codes and the foods that we've included. So if you see data for vegetables, there are vegetables that are not included.

Briefly, I want to try to go through the limitations of food consumption data. These are theoretical limitations. They might be as severe for risk assessment purposes, but it is important to include them and to include assumptions that we hold that would address them. First of all, we're talking about one or two days of eating. Funds are not available to monitor people for two weeks or a longer period of time to tell what they eat over time.

Underreporting and overreporting. We don't know if people ate a quart of ice cream and didn't put that in there or possibly--I know that the data collectors do a lot with portion size, but possibly someone ate more or ate less than what they said. Our assumption is that there are no reasonable corrections that we can use to account for only

one or two days of eating or for underreporting and overreporting of the amount eaten by U.S. consumers. We note those limitations in the data.

Individual ingredients from mixed dishes. You don't just go to the data and put tomatoes, raw tomatoes, and get everything. You have to go in and in order to estimate the consumption of raw vegetables, we included raw vegetables consumed alone as well as those used as ingredients in salads and other foods. Now if you look at the food codes for the raw vegetables and then there's a little combination code that goes along with it, sometimes they did pull in data from salads or from sandwiches or other dishes, but we wanted to try to make sure that we weren't missing anything.

So the process to determine consumption of raw vegetables, we looked at food codes for raw vegetables consumed alone plus those for raw vegetable salads and again those are the raw vegetables that we have included thus far. Mushrooms are not in there. I know there was one sporadic case of listeriosis, but I think it was some kind of homemade mushrooms that--I'm not sure.

Secondly, we used generic salad recipes provided by CSFII. We found the percent contribution of each raw vegetable to the weight of the total salad. This is one

example. There are several food codes for coleslaw. I don't usually make coleslaw and I don't put carrots in it when I do make it, but this one does include cabbage, carrots and onions. If you add together the vegetables you see 81 percent of the amount eaten of the coleslaw would be something that we would pull out and put in the risk assessment. We would not include salad dressing.

Okay. Thirdly, we merged the gram consumption for the raw vegetables consumed alone with the proportion of the vegetables used as salad ingredients.

Okay. Next, back to assumption seven. It says we will model exposure of Listeria in raw ground beef by estimating the consumption of ground beef that is not fully cooked in burgers and ground beef patties. Quickly, the process again, we figured out the food codes for the ground beef patties and for the burgers, looked at burger recipes, determined the percent contribution of each meat pattie to the weight of the total burger. 43 food codes for burgers, cheeseburgers, hamburgers and each food code has different recipe so we had to go in, find out how much beef was in the burger and merge the gram consumption. And the model will correct for the proportion of meat that is not cooked.

And I'm not sure exactly what process we will use, but back in May I showed you this slide that '95-96 CDC

survey indicated that just under 20 percent of the respondents reports that they eat pink hamburger and we don't know how much of the burger was pink. But that was an assumption that we included several months ago and I don't know that we will use this, but we will have some way to come up with a proportion.

Assumption 13: in looking at consumption of hot dogs and bologna and the dry and semi-dry fermented sausage, we looked at those meets consumed alone as well as those used as ingredients in sandwiches.

Okay. Another limitation is small sample sizes. This might not be as big a deal for risk assessment purposes, but the data collectors do say that small sample sizes are a limitation.

Assumption 14: statistics based upon small sample sizes may be potentially unreliable. Weighting data from small samples does not increase reliability. We note those limitations inherent with small samples, but sometimes that's the best we have.

I'm going to show you a few slides, not to try to memorize or get any of the numbers down in, you know, concrete, but there are--this is for eating occasions for five of the groups out of the 12 or I guess I could say 13 that we're currently using. And so, for example, just for

raw fish, there were only 27 eatings for both surveys and we're talking, you know, 47,000 people.

If you weight the data, and again they say you can use the data but make sure you have a footnote that says that small samples, you see that it looks like it projects to a lot of individuals. And there's differences between the surveys.

Okay. The number of eaters--okay--out of the 27 eatings or meals of raw fish, there were 22 eaters for both of the surveys. Okay. So this is raw fish, ready-to-eat fish, smoked fish, soft cheese, and goat and feta. The soft cheese is actually the Brie, Camembert and blue cheese. Okay. And then the weighted numbers again. Those small samples or smaller samples do project to a number of people. Okay.

These eight foot categories are up here and if you look at the per person per day consumed, you can figure out the percent of population eating. If you look at the first six, 99 percent of the population have not even reported that they ate those foods. Okay. The raw fish, ready-to-eat fish, smoked fish, ready to eat shellfish, soft cheese and goat feta, just in case your eyes are going like mine and you can't see the names up there.

For dry sausage and meat and egg salads, there were more eatings, but it's still not a large proportion of the population. Okay. The per capita per day is going to take into consideration the eaters and the non-eaters. And if you look at these, this is not a lot of these eight food groups or foods consumed in the country.

Okay. I just threw in this one slide with the raw vegetables, the ice cream, the hot dogs, bologna, cooked, ready-to-eat meats and burgers and you can see that again if you look at the entire population, which for CSFII, they used 261 million and NHANES is less than that. You see that there is considerably more eaten of these food groups. Okay.

Fifth limitation, there are different weighting factors and sampling designs for each survey. I would like to show you two slides, not to go into great depth, but just to show you that even though there is a small, relatively small sample for these cheeses, the distributions of the eatings, now what this is, these are weighted percentiles. The slide doesn't include 50. The 50th percentile is along the bottom, the X axis. That's the median. Okay. If you go up the left, you see the amount eaten in grams, and if you think in terms of ounces, 28.35 grams would be to the ounce and so it looks like most of the eaters reported that

they ate three ounces or less of these foods. So there were not a lot of eaters and they didn't eat a lot. Okay.

This second slide, and I'm only going to show you two. I had 13 in there and everybody said, no, you don't need to do that. You can see that for raw vegetables that the distributions match pretty well for the two surveys. It's a different scale from the previous slide. It gives 200 grams on the Y axis and you can see that most people who report that they consume raw vegetables would eat that amount. In the tails, it tends to be different.

But CSFII experts said that they would really like people not to even use anything above the 92nd percentile, but we do. Okay. And we're not the only ones. I guess EPA does their regulations based on the top tail, too.

Okay. The last assumption I have listed is we expect distributions to vary to some extent, especially those with smaller samples. Weighted distributions of the larger samples appear to vary less. We did not do statistical testing to determine if the distributions are the same. If you're working with 22,000 data points from one and 18,000 data points from another, it just doesn't make sense, but to follow on, it says we will attempt to use data from both data sets as we deem appropriate and I know

that our modeler, Clark Carrington, has included data in very legitimate ways from both data sets.

Okay. The last limitation, merging food consumption data with contamination data is a given. Conclusion: our commitment is to provide scientifically based, strategically-planned estimates. We're using the best U.S. food consumption data available. We're considering the limitations. We are including assumptions for everyone's review to try to make it as transparent as possible. And we're attempting to reduce uncertainty as much as we're able.

This one just is an extra slide. What do we do with Listeria implicated in other foods for which we have no quantitative contamination level data? Except for the raw meats, we can fill in most of the gaps with consumption data, but we need the contamination data first. Okay. Thanks. Are there any questions?

CHAIRPERSON WACHSMUTH: Clarification questions anyone? David?

DR. ACHESON: The data that you presented was for consumption of the population as a whole. Are you planning to break that down into some of the high risk groups, the elderly, pregnant women, for example?

DR. BENDER: We have provided data with those variables included and hopefully that's going to happen, but I'm not sure if that will happen by December 1. I probably shouldn't say that.

CHAIRPERSON WACHSMUTH: Mike.

DR. BENDER: We're to have a final, but hopefully it will be an iterative final, whatever.

DR. ROBACH: I have a question about your I think it was assumption number seven talking about the ground meats again.

DR. BENDER: Okay.

DR. ROBACH: Ground beef.

DR. BENDER: Who is speaking? I'm sorry. Okay. Thanks.

DR. ROBACH: If I understand you correctly, you were going to model using raw contamination numbers?

DR. BENDER: Raw contamination numbers and then--we don't have data of people saying that they ate raw ground beef.

DR. ROBACH: Right.

DR. BENDER: So we were going to attempt to look at the burgers and then the modeler will include some sort of factor to try to pull out the proportion of the burger that would not be fully cooked.

DR. ROBACH: Would not be fully cooked. My question is are you going to model based on raw numbers or are you going to model based on an end-point temperature that might be less than fully cooked?

DR. BENDER: I would like Clark or someone to answer that at some point.

DR. CARRINGTON: I'll get to that.

DR. BENDER: He'll get to that. We're one part of it. And I'd like to learn how the rest of it goes myself.

CHAIRPERSON WACHSMUTH: Okay. Any other? Peggy and then Spencer?

DR. NEILL: I'm wondering if you adjust for seasonality? I'm not sure how you take that into account for looking at consumption?

DR. BENDER: I understand that these surveys are conducted over all days of the week and over all seasons. I don't, I can't say that with definitive proof, but isn't that true? But I have no clue of--I mean we could pick out what day of the week or what meal the foods were. It could have been breakfast, lunch, dinner, snack, but I'm not sure that the surveys tell what time of the year although they did collect the data over all seasons.

Well, I know like Wes Long said the other day, well, he sees lots of smoked fish during the holidays, but

I'm not sure that we can capture that. I mean possibly if we did--if there were a survey to collect consumption practices of people during the holidays, it might be different.

CHAIRPERSON WACHSMUTH: Okay. Spencer.

DR. BENDER: The data collectors would not have weighted based on that.

CHAIRPERSON WACHSMUTH: Okay. Spencer.

DR. GARRETT: Thank you. Spencer Garrett from the National Marine Fisheries Service. In the final assessment itself, will those appropriate statistical combination techniques--

DR. BENDER: You know I'm sorry. I can't hear.

DR. GARRETT: Spencer Garrett from the National Marine Fisheries Service. In the final assessment, will the appropriate statistical techniques that you referenced for combining the estimates from the two different studies with the 22,000 data points and the 18,000 data points, will those techniques be described in the final assessment? Those techniques that were used?

DR. BENDER: I believe that Clark will be very definitive with what he has.

DR. GARRETT: And so that would be described for transparency purposes?

DR. BENDER: Hopefully, yes. I would say yes.

DR. GARRETT: Thank you.

CHAIRPERSON WACHSMUTH: We're getting a nod from Wes Long as well. Cathy?

DR. DONNELLY: Mary, analogous to what you're proposing to do with the undercooked hamburger, did you consider doing something similar for poultry?

DR. BENDER: Yes, I have considered it. It hasn't gone much further than that, just not knowing exactly what to do, because, you know, we have included the cooked poultry, but again trying to determine cooking behaviors, I mean it doesn't come from the consumption data. It's going to be something else. I mean I know that we have some other homework to do to try and get to some of the trade associations and try to get--but I know that's a really important point. Yes.

CHAIRPERSON WACHSMUTH: Katy.

DR. SWANSON: Katy Swanson. Do the survey data provide an opportunity to look at differences in geographical areas? For example, seafood is probably eaten at a higher prevalence on the coasts than it is in the middle of the country.

DR. BENDER: Is there regional--Eric Hanson--okay.

DR. HANSON: Yes, there is, but it's just broad. Western United States, northeast, areas like this. You cannot go into state or county level or anything smaller than that.

DR. BENDER: Okay. And if you recommend that we include that, we'll include it.

CHAIRPERSON WACHSMUTH: Okay. Could the last speaker who helped answer that question, please identify yourself for the record?

DR. HANSON: I'm sorry. Eric Hanson of FDA.

CHAIRPERSON WACHSMUTH: Thank you. Okay. Bob and then we probably need to move on. We'll have the general discussion shortly.

DR. BUCHANAN: Mary, for those where you either have a very small sample size in your data bases or for where you don't have any at all, can you alternatively use yearly production data as an alternative way of estimating the number of servings consumed?

DR. BENDER: The jury is still out on that one. I am an applied statistician who works in the midst of a lot of nutritionists and chemists and they are appalled that anyone would look at production data and determine what people have eaten because there is a lot of waste, various reasons. But sometimes that's going to be all that we have.

It's just like Dick and I were talking yesterday about raw milk and pasteurized milk, and so possibly we could look to determine what percent is produced of the raw milk and then make comparisons to all milk and then work with those data.

So the possibilities are endless. Coming up with something that is error free isn't going to happen, but I know that there has to be data. It's just like for fruit. One of our team members collected data from American Frozen Food Institute and from Produce Marketing Institute and looked at some agriculture data to try to figure out what proportion of these fruits and some vegetables are consumed or put into the raw market, go into frozen food or go into canned or whatever, and we still have those data, and we have other data like that, but we have not done a comprehensive review of the market.

So if there is something specific that you all would like to recommend, we will definitely look into it, and we are talking about it. We're just talking very quickly because time is moving and, you know, it takes time.

CHAIRPERSON WACHSMUTH: Okay. I think it's time for our next speaker on that note. Clark Carrington, our modeler.

DR. CARRINGTON: Hi. I'm Clark Carrington. I guess I'm responsible for putting everything together. And

I'll give a brief overview on how I'm planning on doing that. I'm looking for my overall. It's not there. All right. Okay. I'll start out by describing a slide I don't have which--and hopefully I will get it by this afternoon. I'll have another chance this afternoon and I'll show it to you this afternoon.

But I have a flow chart showing the overall flow of the model which has, I'd say, approximately 15 boxes which are all strewn together. And so far you've heard talks about two of the boxes which are the concentration of Listeria in food and the distribution of, actually you've seen maybe three of the boxes. The first box is Listeria in food, concentration of Listeria in food. And then there are two boxes which are related to consumption. One is the distribution of meal size, which is largely what Mary talked about, and then also we'll get the number of meals per capita which will also come into the calculation later on.

Then there's a couple other boxes which are part of the exposure assessment which I'm also going to go through here which pertain to--there it is--right there--okay. Got it. All right. The other two boxes, I'm going to--or the other boxes that I'm going to talk about are these ones that pertain to growth. We have a growth model

which right now I'm intending to represent growth from retail to consumption, between retail and consumption.

And that's influenced by time of storage and storage temperature. And so what I'm going to do this morning--I'm going to go through--I'm going to stop at this box called LM per Meal. That's the end of the exposure assessment. All right. Now let's go back. I know what happened to my slide. Wes took it.

[Laughter.]

DR. CARRINGTON: All right. Okay. All right. I'll start out by talking about meal size distribution. I think so maybe I'm going to answer one of these questions. You can comment on whether you think this is appropriate or not, what I'm doing with the NHANES and CSFII data is pooling it, which in virtually no case, you know, makes much of a difference whether I used each independently or combine them. In most cases, they're exactly the same. The only case where it's an issue at all is where you have small sample sizes, and even then it's not a very big issue, and I'll show that later.

I did two different things with the data. With the small data sets, where you have fewer than a hundred sample sizes, I did fit a distribution to the data. For the large data sets which is about half of them, I'm going to

use them by direct sampling from the data set, with weighting of demographic characteristics.

And just to--let's see--next slide, please. Okay. Here's an example of fitting the distribution to the data. I fit three different distributions and they provide somewhat different fits. I'm using these three different models to represent model uncertainty where in essence all three models are used to make the prediction and the discrepancy between the models is used as a source of uncertainty.

I think next slide, please. All right. And I'll just talk a little bit about that. Model uncertainty also goes by the name of scientific uncertainty. It's really not a statistical concept of probability. It's not based on frequency. And to express model uncertainty, you use what's called a probability tree where each model gets assigned a probability, which determines how the weight is given in making a prediction.

And here's where the classical example of model uncertainty. This is a cancer risk assessment exercise where five different models make very different predictions and if you're doing model uncertainty, you use those five different predictions to express the range of uncertainty. And in picking a model, ideally the data will pick the model

for you, but if that doesn't happen, then the other things you think about is the complexity of the model is more complex than is justified by the data. Or is there theoretical support for some of the models? And here is just some software code. This is what the probability tree looks like when you put it in your simulation.

And in this particular example, all the models have been given equal probabilities, but I don't usually do that. All right. Back to the meal size distribution. Here is--these are the fitted distributions and there are two reasons for showing this. One is just to point out the ones that I have distributions for so there is a list of categories there on the left that I have distributions for. The other thing I'd sort of like to point out is there's not a huge difference between these distributions. They're all relatively, they're all within a factor of two or three which as you'll see as I go on is not a big deal. What that means is that meal size is not a big determinant on whether or not somebody gets listeriosis. It's other factors that matter a lot more.

And these are empirical distributions which basically these percentiles come directly from the data set rather than coming from the model. All right. The other thing we're getting out of these surveys and we don't

necessarily have to get this out of the survey, but right now we are, is meals per capita. And this is going to be used to estimate from a given food category how many meals we're getting per annum at each dose from a given food source. And right now we're basing our estimates our estimates on the consumer surveys. Since we've got two independent estimates, we're using those which aren't that different--they are quite similar--we're using those to bound the uncertainty on the estimate.

And when I say--I say rectangular distribution several times in this talk. Rectangular distribution is basically the simplest distribution where you have a range where any value in between the range is equally likely. And I guess--and explain the other distribution, I think I talk about is a triangular distribution. A triangular distribution is described by a central value which is taken to be the most common and most likely depending on whether you're using it as frequency distribution or an uncertainty distribution. And then it also has two tails which are the minimum and max. And it's like a rectangular distribution in that you have basically two straight lines or two--the probability between them being most common and the two tails is distributed equally.

All right. To move on to Tony's subject, I also modeled Listeria concentrations at what I'm taking to be retail and whether it is or not, you know, perhaps there are some samples in there which are either not quite retail and perhaps some correction should be made for them. I think that's an open question, but at least for right now, we're treating all those as if they're what comes out of the store.

And then I guess the other thing I can say about this is any data that Tony has put together is in a way a default. You know if we have data that is more specific for any particular, you know, food category--in other words, your food--then that would supersede anything that we got elsewhere. Most of the data we got has been collected from all over the world. A lot of studies aren't even in very good agreement with one another and so we look at them as crude generalizations that we'd love to be able to replace with better data.

All right. Another thing is and the key point on this slide is that the way I used absence/presence data is I used it as a data point which is determined by basically one over the sample size so that if a negative value obtained with a 25 gram sample means that the level in that sample

was less than 0.04 cfu per gram. And if it's 100 gram sample, it means less than .01 and so on and so forth.

All right. I also fit with three different models and I sort of picked this one as kind of a worst--it's probably the worst case in terms of lack of agreement between studies, but basically these points down here at the bottom are from one study and then we have some other ones that are considerably a higher percentage of them are negative and then there's another study that's sort of in between.

And also I fit three different models and the three different models give fairly substantially different predictions. And you can see that, you know, none of the models are really fitting the data points because they're really sort of integrating the results from different studies.

And I don't expect you to look at the numbers here. This is mainly here just to show you the categories I have distributions for now. All right. The next step is to model growth and this step is intended to model growth basically in the hands of the consumer. That's how I currently envision this box. And I'm using the USDA pathogen modeling program and I still think it's an open

question as to what extent this program models, you know, various food categories.

For example, Tony showed some data suggesting that concentrations in cheese actually go down after you add Listeria rather than up. And I don't know how universal that observation is either, but that's not what the pathogen modeling program predicts. If you add a bug, the concentration always goes up.

And let's see. The one source of error that is included in the USDA modeling program is sampling error, which is based on the original experiment that the model is based on. And let's see. Then there's a couple of inputs that go into the modeling program which are particularly important. One is the storage time. And right now we, Dick and I, just put together a distribution which is basically based on our personal experience, and again we'd love to have something--also right now we're using this sort of as universal distribution for all foods.

If anybody has any data, it's either, you know, that describes consumer behavior with regard to a particular category, we'd like to have that. And the other input is refrigerator temperature. We do have, we're in better shape on this one, I think. We do have a survey of U.S. refrigerators. And we're using that basically as is by

sampling percentiles directly from the data, which means there is no uncertainty associated with this part of the model.

All right. Then we've got a box in there for the effect of cooking and the main reason for having that in there right now is for the hamburger issue although it may also be, you know, become important for some other food categories as well. Right now the way we're envisioning--I mean I've got a very simple model in there which is sort of based on the one piece of data I was given which is that 80 percent of the hamburgers consumed in the United States are fully cooked. So I'm using that to generate a distribution where 80 percent of the hamburger will undergo a full kill and then the remaining 20 percent has a partial kill, and the distribution that I currently have in there is a distribution ranging from either zero percent survival to either 20 to 60 percent survival where this 20 to 60 percent is an uncertainty bounds so that ends up contributing to a source of uncertainty.

And obviously there is--if you have a model which will relate--clearly this could be made more sophisticated. I mean I think somebody brought up temperature. For instance, the more sophisticated you make your model, the more information the manager has. So, for instance, you

could have a temperature model which will predict the number killed as a function of temperature. The thing you're going to need to have a nice survey of hamburger temperatures as cooked in the U.S. population which is a pretty tall order.

But maybe we have that. I don't know. If somebody has that and can give it to us, we'll use it.

All right. I guess now I will talk about how all the segments of the model are put together. And I'm going to do this now because I'm only going to show you a simulation for the exposure part of the assessment. I think the dose-response is a little behind the exposure part so I don't have a full model that integrates all the parts of the dose-response assessment.

And the way I'm going to do that is with what's called a 2D Monte-Carlo. And this is not real computer code. This is pseudo-computer code which sort of outlines the logic in how a two dimensional Monte-Carlo is conducted. The idea is that there are basically two sorts of distributions that we want to integrate separately, one o which is--some of the distributions are intended to describe actual population differences or actual differences among food samples. In other words, they're frequency distributions.

And then on the other hand, we have some other distributions which are probability trees which are intended to describe uncertainty which is rather than describing what we know about differences in food samples, it's talking about what we don't know. So we have--to keep those two types of distributions separate, we do not a one-dimensional simulation but a two-dimensional simulation where first you go through and resample all the uncertainty distributions, then you run a frequency simulation, and you do that by using a computer loop where in the outer loop, we're resampling the probability distributions. And then we get to the inner loop where we resample the frequency distributions, calculate the model output and then store that value in a two dimensional array.

So at the end of this entire process, you end up with this two-dimensional array where one dimension is uncertainty and the other dimension is frequency. And here's a table which sort of gives you the idea that you get a lot of numbers out. Like I do 10,000 frequency--I usually do more frequency iterations than uncertainty iterations, but if you do 10,000 frequency distributions by a 1,000 uncertainty reiterations, you can get ten million numbers out.

And this is--all right. Here's a table. And I'm going to condense this. Just to show you some actual results I condense it to that. And first of all, for this cheese simulation, I just concentrate on the upper ten percent. In other words, I truncated the frequency distribution so I was only looking at values between .9 and 1 because it's only the upper ten percent that have any Listeria. Therefore, my simulation ended up starting at 90 percent. And then I've condensed the uncertainty distribution to basically a median and a lower bound which is the fifth percentile and upper bound which is the 95th percentile.

And I guess the conclusion from this is if the growth model is right and you get a fair number of cheese samples with, you know, the growth model and the contamination data--I think are the two mean areas for contention--Listeria in cheese data--then you do, you know, not infrequently get whopping numbers of Listeria in the cheese. All right. And I guess that's the end of the exposure assessment. Right.

CHAIRPERSON WACHSMUTH: Okay. Thank you, Clark. If we have one question, I'll take it. Otherwise, I think we'll take a break and then we'll bring all of the speakers

back for the questions and discussion. Okay. No quick questions. So let's take a break for 20 minutes.

[Whereupon, a short break was taken.]

COMMITTEE DISCUSSION

CHAIRPERSON WACHSMUTH: Okay. Now if the presenters would like to sit up front at the table near the podium, then we can open the floor to any questions. Bill.

DR. SPERBER: Yes, I'm Bill Sperber. I have a question probably directed more toward Tony Hitchins than the others. It has to do with the selection of the food categories for inclusion in this model. And I believe one of the sources of data you used for determining the food categories were recall data. And one thing that leapt out of your presentation suggested to me that perhaps in the final analysis, you should not rest strictly on these recall data because I believe you need to make a distinction between what I would call a public health hazard and a regulatory hazard. Sometimes foods are recalled not because of any public health implications but because they are somehow illegal or they are somehow the subject of regulatory scrutiny.

And one of those categories of food is ice cream. It's permanently included in your survey. So far there have been hundreds of recalls of ice cream products since 1986. I

don't know of a single illness attributed to ice cream and in my experience I would submit there never will be a case of listeriosis caused by a commercially produced ice cream. So I would just--there may be other categories of foods i your preliminary work here that similarly could be described as a regulatory hazard and I would encourage you as you go toward the final risk assessment model to perhaps exclude those categories of food from your model.

CHAIRPERSON WACHSMUTH: Tony.

DR. HITCHINS: I don't know if this is on. Can you hear--yes, it is. Okay. We didn't have any recall data in the database.

CHAIRPERSON WACHSMUTH: I think I was confused initially as well. Are we talking about a regulatory recall? Are we talking about recall information from a survey? Consumer recall is what Dr. Kvenberg is saying. Could you clarify that? Does that help?

DR. BENDER: When we initially attempted to identify foods that were at greatest risk for contamination that was one source of data. So that was in our initial breakdown or--

CHAIRPERSON WACHSMUTH: What does that mean? What was the source?

DR. BENDER: The source?

CHAIRPERSON WACHSMUTH: You said that was the source. Would you define "that"?

DR. BENDER: Okay. The recall data are available from various sources like on internet there are--oh, gosh--I don't know. There are a couple web sites that would list the FSIS recall.

CHAIRPERSON WACHSMUTH: Oh, so these are regulatory recalls. Okay.

DR. BENDER: Right.

CHAIRPERSON WACHSMUTH: Does anyone want to speak to this point? Mike.

DR. ROBACH: Yes, I wanted to ask a question. They were regulatory recalls for what cause? Were these specifically recalls for Listeria or were they--

DR. BENDER: Yes.

DR. ROBACH: --general recalls for everything?

DR. BENDER: No, there were for Listeria.

DR. ROBACH: Specifically for Listeria?

DR. BENDER: Right. Sometimes a company recalled their product. Sometimes FSIS or FDA asked the seller or whatever to recall the product, but there was never--in any noting that I've read, I never once saw this has been connected to listeriosis. It was simply presence of listeria in a product. And I know that the data that we

just received from International Dairy Foods Association, all of the testing for ice cream did, it was negative, but there were some frozen dairy products where some of their members did identify that they found listeria in the product, but it was all presence/absence, and it was not linked to any sort of health hazard and we are aware of that.

CHAIRPERSON WACHSMUTH: John Kvenberg.

DR. KVENBERG: Yes, thank you. John Kvenberg. Mary, I think part of our confusion or the confusion of the presentation was your talk where you were speaking with the term "recall," and it is true that in your presentation, you were talking about the consumer's ability to recall the meals they ate over two days? I think that's part of the confusion.

DR. BENDER: Oh, okay. Sorry. No. This strictly up front when we were identifying the ready-to-eat foots, primarily ready-to-eat foods that were at greatest risk, we wanted to see, first of all, what had been implicated, whether it was listeriosis or whether there were--there were lots of articles that Tony scoured and I scoured on some set of that where researchers identified Listeria monocytogenes and then just looking at the U.S. recalls, not--that was the purpose. That was their use of the term.

DR. KVENBERG: I'm sorry. But you didn't understand my point. In your specific presentation on the NHANES data--

DR. BENDER: Right.

DR. KVENBERG: And other information when you were discussing information on recall at that point, were you not talking about the ability of the consumer to answer the survey?

DR. BENDER: Oh, you're talking about dietary recall?

DR. KVENBERG: Yes, ma'am.

DR. BENDER: Oh, I'm sorry. Ah, okay. What should I say? What do you want me to--

DR. KVENBERG: Well, just to eliminate some of the confusion.

DR. BENDER: Confusion.

DR. KVENBERG: --that went around the table here.

DR. BENDER: Thank you.

DR. KVENBERG: That you were referring to the ability of the consumers to recall the meals they ate--

DR. BENDER: Right.

DR. KVENBERG: --in that part of the presentation. Is that true?

DR. BENDER: Right. With the overreporting and underreporting. Some people might not remember exactly what they ate.

DR. KVENBERG: Thank you.

DR. BENDER: Thank you.

CHAIRPERSON WACHSMUTH: We have several people. We have Peggy, then Katy, then Roberta, then Alison. Peggy?

DR. NEILL: I think in carrying on this confusion over the term "recall," then could Tony clarify whether the data from recall of food of food from marketplace is inclusive of recalled product not linked with cases as well as or separate from recalled product linked with human illness?

DR. HITCHINS: Yeah, I should make it 100 percent clear that in the contamination data set, we don't use recall data. All that data came from the literature, scientific literature. It's samples of various foods analyzed by various laboratories to see whether Listeria mono is present and sometimes whether, how many numbers of it are present? We're not using recall data to the best of my knowledge.

CHAIRPERSON WACHSMUTH: Just to eliminate any potential confusion that's still out there, are you satisfied now, Bill Sperber?

DR. SPERBER: I think the term "recall" here has been used in both senses, product recalls--

CHAIRPERSON WACHSMUTH: Correct. But the contamination does not include regulatory recalls.

DR. SPERBER: --and dietary recalls and I think my question was correctly framed in the first place.

CHAIRPERSON WACHSMUTH: Okay. We'll finish the questions here and then maybe we'll break down the questions to the different modules. That might help us organize it a little bit. Katy?

DR. SWANSON: I pass.

CHAIRPERSON WACHSMUTH: Roberta.

DR. MORALES: Yes. This is more a point of clarification and part of this may be because I was not at the May meetings. My recollection from February was that initially a quantitative ranking of these different food products that were considered potentially linked to Listeria monocytogenes were going to be evaluated and from that ranking and evaluation, a subset of those food products were going to be then selected as candidates for further quantitative risk assessment.

I didn't get the sense here that that was what was going on in that in some sense the food categories were selected based on availability of data. I wonder if

somebody could make that clarification and why the shift from February till now?

CHAIRPERSON WACHSMUTH: I think that's a question for Dick or Wes either? Or Tony?

DR. HITCHINS: Well, I can just comment that I really don't know anything about what transpired in February except what you've told me. My impression is that the data collection is to cover all foods, particularly ready-to-eat foods with special emphasis on ready-to-eat foods.

We want to know how much Listeria monocytogenes people are consuming in the U.S. and that will mainly come from ready-to-eat foods rather than cooked foods obviously. There was no intention--at least when I started, I was not given instructions not to consider all ready-to-eat foods, not just concentrate on soft cheeses or smoked fish, but to consider all of them.

CHAIRPERSON WACHSMUTH: I think you were correct in part, but, Wes, did you want to--

DR. LONG: Roberta, I think you're right. Back in February, we had not completely formalized our charge with our risk managers. By the time the Federal Register document came out in April or in May, then that was further clarified. So there may have been--those comments in February may have been preliminary, but that is not what we

have pursued, even if we did say it in February, and that we will, you know, so this is a comprehensive effort across all foods, all sources of contamination, all sources of exposure. Perhaps we'll be asked, once this process is done, to target specific foods and then we'll go back and look at those more closely.

DR. MORALES: In that regard then as far as the food categories that are included in evaluating the exposure to LM, how do those jive with epidemiological data from CDC or information we know about certain categories of foods or certain food products that are very closely associated with LM? And is there a correlation between those two between what you've found now and what some of that information we know about epidemiology of LM is?

DR. LONG: I think--this is Wes again--I think the correlation that needs to be drawn is that from the food consumption side, we tried to find all of the foods that had ever been associated or implicated with Listeria, with listeriosis as well as with Listeria from recall data. So that was to try to identify the, as best as we could, from data what the universe was of foods that had the potential to be contaminated. That's one side of it.

The other side is the data of actual contamination surveys and so there are places where those two things don't

match up. There are no Listeria contamination incidences from outbreaks from which there is no survey data. There is also some survey data--I'm assuming; I don't know for sure--there may be survey data where there has never been an association with any sort of recall or illness or epidemiological data. But the challenge is to merge those two things together.

CHAIRPERSON WACHSMUTH: Okay.

DR. LONG: And to stay where we have data. If we don't have data, unless someone can provide us data and we'd be happy to take that data, then there is nothing we can do in order to remain quantitative.

CHAIRPERSON WACHSMUTH: Alison?

DR. O'BRIEN: I have a question of Tony. Tony, you had asked us to consider alternate methods that might help you look at incidence in food and what possibility was to look at other Listeria species. That was one point on one of your slides. What data do you have that says that you could look at other species and then either make a correlation directly with Listeria monocytogenes contamination? For example, if there is a certain level of the other species in the food, that would suggest that you might have 15 percent of the time you might have L.

monocytogenes. Do you have any data like that that says A and B are linked?

DR. HITCHINS: We have data where Listeria, total Listeria was enumerated, and then as a subset monocytogenes was enumerated, several studies like that where one can then derive some kind of correction factor to go from total Listeria to monocytogenes.

DR. O'BRIEN: Then to follow up on that, among those studies, was there consistency in the percent that would be L. monocytogenes among the total Listeria contamination?

DR. HITCHINS: Well, I haven't tabulated all the data so I can't really precisely answer your question, but my impression was that, you know, a third or more of Listeria incidences were due to monocytogenes, but I take your point that if we use that kind of correction, we would want to carefully look at available data for the particular food or food class that we want to use the correction for to make sure there is--some food isn't selective for total Listeria as opposed to mono. Yeah.

DR. O'BRIEN: Yes.

DR. HITCHINS: Other species of Listeria as opposed to mono--

DR. O'BRIEN: Could I ask one more point of clarification from Tony's presentation? In your, back to your issue of density on your slides, which I understand was really a reflection of how many times you found studies that gave enumerative data, did the enumerative data actually include an attempt to make a count and not finding anything? Did you include that as part of your density?

DR. HITCHINS: Yeah, yes, it did. And I apologize for perhaps misleading several people in the audience. The numbers under density are the total samples that were involved in a study that enumerated monocytogenes and therefore would include the category of no detected Listeria, 100 or more Listeria, 1000 to 10,000 Listeria, et cetera. Okay. Is that clear?

DR. O'BRIEN: Yes, that's clear.

DR. HITCHINS: I could have clarified that, of course, by giving another column with the percent Listeria in those samples that had been enumerated and you would have seen then that it wasn't going to be 100 percent. That would have clarified it.

DR. O'BRIEN: I have one more question of you and you may not be able to answer this. But from studies where you looked at enumerative data, when you had enough samples to make this assessment in your mind, did any particular

foods stand out as having higher levels consistently? Higher levels of Listeria monocytogenes?

DR. HITCHINS: I haven't done that analysis precisely, but my impression is no, you know, no, at least amongst the foods that, you know, support growth of Listeria, yeah.

DR. O'BRIEN: Thank you.

DR. HITCHINS: Yeah.

CHAIRPERSON WACHSMUTH: Swami.

DR. SWAMINATHAN: I have two. Bala Swaminathan, CDC. I have two comments and a question. I wasn't present in Chicago so this may have been discussed already, but I think it's an important point that needs to be reemphasized even if it's been discussed. Listeria monocytogenes is ubiquitous in the environment and it is also found very frequently in the food processing environment. Given that, I think using consumption contamination data and modeling to determine the risks to the general population may not be all that instructive and I think this group needs to in addition to what they are doing, definitely needs to target those groups, those people in their risk assessment that Listeria targets. That would be the immuno-compromised. As you know, Listeria prefers to attack those people who have

either a local immune modulation as in pregnancy or general immuno-compromise situation.

So I didn't hear anything this morning that all of this effort is going to include those groups specifically and I think that risk information is extremely important for the risk managers to come up with any reasonable decisions.

The second comment I have is to support what Dr. Cathy Donnelly mentioned, the 1989 sporadic listeriosis study specifically mentioned undercooked chicken as one of the risk factors and I think just like you have done for the hamburgers, you need to include the undercooked chicken in your modeling.

The third question for--I mean the third item and a question for Tony Hitchins is you mentioned that you were not at this point including subtype information. I think serotype information is extremely important in your modeling and everybody will be interested to know the risk for serotypes 1/2a, serotypes 1/2b and specifically serotype 4b.

DR. CARRINGTON: All right. Most of the issues you just brought up we're going to go over this afternoon. So those are all part of the, at least that's just the way we grouped it. It's part of the dose-response assessment so that we're going to make some adjustments for host susceptibility, strain virulence, prior to the dose-response

assessment and those boxes were just artificially grouped into that part, partly because they do involve interaction with the host. So that's the rationale for that.

So I guess since we're going to talk about it this afternoon and I do have a presentation on it, I guess how about holding that for later.

DR. LONG: In terms of--Wes Long again--in terms of the poultry survey and the undercooking, is anyone aware of any data similar to the data that we have for hamburgers that can help us model that level of consumption of undercooked chicken because I mean again it's a qualitative piece of information unless we can back it up with some data? We're open to that data if someone thinks of a source of it.

CHAIRPERSON WACHSMUTH: Thank you, Wes. Swami? You okay?

DR. SWAMINATHAN: I just wanted to again ask Tony if he had the serotype information that could be provided to the modelers?

DR. HITCHINS: Yes, we have some serotype information, but we haven't looked at it closely so I can't, you know, be definitive. There is serotype information available, but I'm not sure how much of it is there and how well it's distributed amongst the various food types. We're

not saying we're not going to look at that. It's just a secondary part of the study, I believe, yeah.

DR. CARRINGTON: Okay. Since it won't wait, right now I guess we're having a hard time correlating serotype with risk. You know what I mean--there is not really any very good data that we're aware of that, you know, clearly indicates that certain serotypes are more virulent than others and therefore we haven't ruled it out or anything, but so far we haven't done. Even, like for instance, there is one study that shows that most of the--the serotype that occurs in meat is of one type but that serotype is very rare in being associated with illness, but then you don't know whether or not that's because meat is usually cooked and therefore it doesn't get the opportunity to produce illness or because of a difference in virulence. I mean there's really no--the one survey we have of species virulence--there's actually a couple, but they mainly look at 4B, a couple serotypes and they're really not--they don't really cover the whole range. And so right now we're kind of stuck in terms of associating serotype with virulence, I think.

CHAIRPERSON WACHSMUTH: I do know we'll hear more on that.

DR. CARRINGTON: That's what I was trying to do, but it didn't work.

CHAIRPERSON WACHSMUTH: Okay. Mike Doyle.

DR. CARRINGTON: Well, the reason it comes up is if we can't tie the virulence to--the serotype with virulence, then we don't have any reason to care about what the distribution is in the food. But once one becomes important, then the other one becomes important.

CHAIRPERSON WACHSMUTH: Okay. Mike.

DR. DOYLE: Okay. This is Mike Doyle. I have a question for Dr. Hitchins. Are you doing anything to segregate out results of studies done within the last maybe up to five years versus studies that have been done a decade or more ago?

DR. HITCHINS: We haven't done anything as yet. I mean we haven't ruled out doing that. We could certainly sort the data or get it sorted it out by date and therefore compare the time line over the last ten, 20 years, yeah.

DR. DOYLE: And you're also lumping all the data internationally with data from the U.S.; is that correct?

DR. HITCHINS: Yes, we have so far, yeah.

DR. DOYLE: Well, personally I have major concern about that because I think today or at least in the last five years, at least certain segments of the industry have much lower incidence of Listeria in products than they had a

decade ago and so lumping that all together may give us some erroneous direction.

DR. HITCHINS: No, I 100 percent agree with you. I mean pooling is a very dangerous thing to do. I mean you really have to look, do the kind of thing you were saying that later we would have to un-pool it, split it up into various time categories or country categories and make sure that the conclusions we draw from the pool are representative. It is interesting though that when you look at the contamination frequencies around the world, I don't see marked differences. One that stuck in my mind was a group of foods they did in Singapore where being in the Far East, one might--I know Singapore is one of the tigers of the Far East and more industrialized, but its contamination rates were not markedly higher or lower than Western industrial countries. You know--but your point is well taken, yeah.

CHAIRPERSON WACHSMUTH: This is just a note from the chair, and it goes along a little bit with what Roberta said. Initially, this was a ranking exercise intended as sort of a rough cut and from that we would do a more refined quantitative risk assessment on specific products and pathogens as Wes said, looking at the whole process on the table and trying to design models that way. If this has

changed dramatically, we need to clarify that. Wes, would you like to address that point?

DR. LONG: I'll let Dick try to do it because he was more closely involved in drafting the charge in terms of what we publicly announced that was the process.

DR. WHITING: I would say that is correct, Kaye. It has stayed with that same purpose. We are trying to put, you know, food categories together of which we have data and we would discriminate as much as we feel we have data to be able to do that. And that's what this one will be. This is will--call it a rough cut. That's probably a good description of it in terms of ranking different food groups because I'm sure people could sit there and look within food groups and say this particular one is probably a relatively low risk and then this other one is high, you know, looking at the vegetables, for example. You know there are data showing potatoes and radishes I think in one study came up high and other vegetables came up low, but we just don't have enough data that we can go through and every vegetable. So it is a broad cut, but then, you know, based on this, then I can see in the future we could go back, be asked to go back and try to look at more detail at specific commodities.

CHAIRPERSON WACHSMUTH: Okay. Good. Thank you. John Kvenberg.

DR. KVENBERG: Thank you. My question is to Tony Hitchins as a follow-on to Alison O'Brien's question on the surrogate issue. Simply put, my memory of the distribution of contamination was Listeria monocytogenes and Listeria inocua [?] were largely the preponderance of species that are enumerated, but in your search of the data, did you see a lot of information that was Listeria, not further identified down to species level, as part of your data set or did you have further breakdown of what was found?

DR. HITCHINS: We had very little enumerative data specifically for Listeria inocua. We had more for Listeria in general and most we had for monocytogenes.

DR. KVENBERG: But I guess my question was would some of your data set include Listeria not identified to species?

DR. HITCHINS: Correct.

CHAIRPERSON WACHSMUTH: Bill Sveum.

DR. SVEUM: My question is for Tony and it relates somewhat to what Mike mentioned earlier. The classifications of some of these foods, the classification of deli/luncheon meat, they are really two different products. And if we think about a perishable product lunch

meat with a shelf life and some of these products could have been two months when looked at versus deli products cooked in the bag. They basically are free of vegetative organisms and they wouldn't be really the same risk. And if we're going to look at exposure to products, those are two different categories of products. They should be separated, deli/luncheon meat.

DR. HITCHINS: Yes. We agree.

DR. LONG: I'll just restate the problem that we have with that which I think we all agree, but it depends on whether we have survey data on deli/luncheon meats.

DR. BENDER: We could probably look at market data and figure out the proportion, but as far as the contamination data, we probably wouldn't know which was which where they had tested the meats from a deli counter versus the other. Is that correct? Yes? No?

DR. LONG: Do we have data for deli counters versus packages?

DR. HITCHINS: I don't think it's clear. No, I don't think so. There may be a few instances where it's defined, but I don't think it's clear.

CHAIRPERSON WACHSMUTH: It seems that we may end up with rough cut is perhaps not the right choice of words

but a broad sweep and we will have to refine it to really get to some answers about risk.

Okay. Next is Mike Robach. I'm going to continue just to take people. We've got about six flags up instead of trying to stop and go to the categories. Go ahead, Mike.

DR. ROBACH: This is Mike Robach. I want to come back to my earlier question about undercooking. I think everyone is fairly familiar with the hazards associated with the consumption of undercooked animal proteins. And I don't know that there is a lot to be gained by spending a lot of time looking at this hazard as well. I think the E.coli O157:H7 issue in ground beef, Salmonella in other meats. We know that if products are not fully cooked that there is microbiological hazards that one needs to be concerned about.

But I am concerned again about the rectangular distribution of survival in hamburgers. You know I think that's a blanket assumption that one is making and now you could make probably some other assumptions like hamburgers are cooked to at least 140 degrees or something like that. Thermal destruction data is available on Listeria, which I think would be of benefit in fine-tuning this a bit more than it is now.

DR. CARRINGTON: Well, my first suggestion is how would you like to develop an alternative and I'll look at it and maybe I'll put it in, and if you don't want to do that, give me some ideas and I'll do it.

DR. ROBACH: Okay.

CHAIRPERSON WACHSMUTH: Okay. Katy.

DR. SWANSON: Yes. I'm going back to the surrogate question. I'd be a little nervous about substituting or trying to extrapolate from species numbers down to LM. Work was published in, I believe, the early '90s, Pietran [?], et al., showing that the growth rate of monocytogenes in commonly used enrichments is different than inocua and inocua will outgrow the mono if it's put in at similar levels. Because of that, most of the enumeration methods tend to be MPNs and it will be very difficult to extrapolate and come up with a number that would be true.

I think it might underestimate the level of LM or the quantifiable number of LM present in a given sample and it might overestimate the prevalence of LM in those samples because there are samples out there that have Listeria species and no monocytogenes. So I'm not sure that that would be a wise move.

CHAIRPERSON WACHSMUTH: Okay. Thank you. Art.

DR. CARRINGTON: There is another step I could take with the modeling of the Listeria data--I mean it would be fairly technically complicated which would make it hard to do by December. I don't know. Maybe I could do it--which is right now, the only source of uncertainty I have there is model uncertainty, but if we had some a priori discussion of measurement error associated with the levels, I mean I think this is--I don't think this is doable by December, and it's also not doable with all the data that's out there just because we'd have to go back and it would make the data reviewed that much more difficult because you'd have to come up with some idea of what the underlying uncertainty with those reported numbers are.

But we certainly could do it in some cases and I think in the long run it might be worth doing that. But anyway, if we have some a priori description of what the measurement error is, then we can incorporate that into the uncertainty characterization I guess is the simple answer.

CHAIRPERSON WACHSMUTH: Art Liang.

DR. LIANG: I had a question about the model. We never have all the data we want, but are there, of these 15 or so boxes, is the model particularly sensitive to any particular one or ones? I don't know if that's a meaningful question. I have a little experience with decision analysis

and in decision trees sometimes one or two, you know, nodes on the decision tree are particularly critical and the rest of those differences don't make a difference.

DR. CARRINGTON: Well, I generally put them in because I think they might make a difference. That's sort of my criteria for including model uncertainties. If I think it might make a difference, I put it in because if you put it in and it doesn't make a difference, well, then it doesn't hurt anything to put it in. I mean when all the models make the same prediction, putting in model uncertainty doesn't make any difference. It's when they make different predictions and for some of those distributions they do make quite different predictions. And in terms of how that will impact the overall risk, that's kind of begging the question because it's a very complicated model and whether or not anything is driven by, you know, the ultimate risk can be driven by--is to some extent driven by almost every box we've got.

I mean I'd say the only one that it doesn't matter very much, I think, is consumption. Actually that's about the only one that doesn't have, you know, at least in some circumstances some potential on whether or not somebody gets sick.

DR. LIANG: And one follow-up to that. In that case, and I apologize if this--being from CDC, we have outbreaks on the brain, but it seems to me in our experience the total number of cases is a function of endemic disease and epidemic disease. So does your model--it's sort of related to Swami's question--does your model account for--it appears to me, not being very smart about this, to be an endemic model versus an epidemic model.

DR. CARRINGTON: I guess endemic meaning?

DR. LIANG: Meaning that you're tracking systematic errors over time, but there are also sort of acute errors, you know, if somebody keeps the food in the refrigerator longer than they're supposed to or something like that, and there's a--but there's a finite probability--we may not know it, but there's a finite probability that that will happen.

DR. CARRINGTON: Well, the storage time is a frequency. Okay. So that there are--that was another, you know, along with that rectangular distribution I had for the cooking, that's another one which--I don't think--it has a little more experience behind it than the other one, but I mean there is a frequency of storage time and that is part of the model. Okay. So that's in there, and some of the risk is going to be driven by the fact that some people keep

things in the refrigerator for a very long time. I think my tail in the distribution is 2,000 hours and maybe that's not long enough, but that's--that is part of the model and that's something to think about.

DR. HITCHINS: If I may comment on that as an aside, I mean we're assuming a sort of a single distribution of frequencies of numbers and no one is to say that it couldn't be as you say there may be two distributions, sort of the normal production storage type of distribution and another one out at the high levels that's sort of a second little peak. It would be very hard to dissect that out giving the variability of all our data. So, you know, I think Clark would probably agree that you really have to go for one distribution if I understand you correctly.

DR. LIANG: That's good. Thank you.

CHAIRPERSON WACHSMUTH: Okay. Dan Engeljohn.

DR. ENGELJOHN: Yes. This is a really a point of clarification. I think this is for Tony. On the days for tenfold increase of refrigeration temperature, was that information provided based on actual data or was that modeling? And then was this also derived from a constant temperature or did it deal with fluctuation and was there a temperature range associated with that as well as

environmental factors like a closed package versus open, modified atmosphere?

DR. HITCHINS: Basically all this data was from the literature. In other words, trying to see what is happening in various foods under various conditions of refrigeration and use that as a check on the model and in the instances in which Dick did make a few comparisons it worked quite well. Temperatures--they were various studies from the literature and the temperatures often varied, you know, I mean five degrees, seven degrees, ten degrees and so on. And also I think that covers all your points. Is there another one? Does that answer your question? Yeah, it's literature data, yeah.

CHAIRPERSON WACHSMUTH: Okay. Mel Eklund.

MR. EKLUND: This is Mel Eklund. Yes, over the period of the last decade the methodology used to identify or isolate Listeria monocytogenes has evolved very rapidly. And this kind of follows through what Mike Doyle was mentioning earlier and that is that the data that may be more recent where the methodology is more sensitive to detection could indicate that that particular product was more of a potential hazard than something that had been done say five, ten years ago, data five, ten years ago.

The other thing of concern that I have is the lumping of all your temperatures, I know, in days to doubling of the organisms--tenfold, I guess, is the increase of the organism that you used--was the fact that there is a tremendous difference in the rate of growth in all these different studies of these different food products. Some of them have been done at four degrees. I mean between say four and seven degrees centigrade is a tremendous difference in the rate of growth. And you go to ten degrees centigrade, there's another tremendous growth. And when you try to pull these together, some foods may look more dangerous because of the temperatures where they were used, incubation was used.

DR. HITCHINS: With your first point, second point first, that was a distillation of data to show you the kind of data we would use from the literature and therefore might be misleading in the sense that you mentioned. I mean clearly--you know, I have a couple of pages of data and I just gave you ten lines that were condensed out of that, selected and condensed out of that. So it doesn't give you an idea or doesn't give us, the audience, an idea of the variability that you mentioned due to temperature and food matrix, et cetera. Obviously we would use the literature

data very specifically if we could to apply to specific modelings.

CHAIRPERSON WACHSMUTH: Dick.

DR. WHITING: If I could follow up on those. These studies from the literature are your classic inoculated pack [?] type studies, but very often you don't have any knowledge of what strain was used or how that strain might be relative to other strains of Listeria. You frequently don't have pH and salt specifically mentioned, and most of the time they only did the study at one or maybe a couple of temperatures. So what we wanted to do then with this is we want to have a growth rate and we have a distribution of refrigerator temperatures. So we want to be able to predict the growth rate at a whole series of temperatures and then we're going to put in a time of storage distribution.

So, you know, some foods consumed within a day or so of purchase and other foods may be kept in the refrigerator for a fairly long period. And Clark has a placeholder distribution in there right now, but we're going to vary that where some foods will have a relatively short life and then other foods like some of your fermented meat products will have a very long shelf life. So we need to

create a Listeria growth model that can account for different temperatures and different storage periods.

So that's why we couldn't use the inoculated pack studies directly because they're just too limited, but we can then use the inoculated pack studies to check how accurate the growth model seems to be for that particular food category. So does that kind of give both Dan and you a little better idea of what we're trying to do there?

DR. HITCHINS: With regard to your chronological question that Dr. Doyle also raised, certainly hygiene has improved over the years so one might expect the contamination rates to go down and counteracting that we might be better able to find Listeria. We're quite aware of that. I think when we get some sort of final results, we're going to have to look back in there and make sure, try to make sure that, you know, there's no effects like that that are misleading us.

CHAIRPERSON WACHSMUTH: Okay. Skip?

DR. SEWARD: Thank you. Skip Seward. I work with McDonald's Corporation. And my question is to Mary. Mary, my question is pretty focused. It's on the basis for the assumption that about 20 percent of the hamburgers that are consumed are undercooked. And it appeared that the basis for that was a survey done of consumers asking them about

whether or not they had their hamburgers eaten when they were pink. And I think it's fairly well known now and, in fact, the USDA actually has published that says color is not a recognized indicator of doneness or product being fully cooked.

So I think if that's the sole basis for projecting such a high level of undercooking in ground beef, I think that that's a bit of a stretch myself, a bit of a problem, if you would. If they would have known at the time and they were able to ask is it raw or undercooked in those kinds of questions, I'm sure that would have been much more helpful to you in your group, but I think just on the basis of color alone, that's not a recognized indicator of doneness. And the only suggestion I would make along this line is that you might, if, in fact, this is primarily consumer data that was referenced--I don't know if they were talking about in home or what you, how you like your hamburgers at home versus how you like them when you're served when you go out because, as you know, with all the focus on undercooking in ground beef, I'm fairly certain that you're not going to see those kinds of levels of undercooking in restaurants that are serving ground beef.

So if you're going to go down this pathway with this consumption data, you might want to break it out as,

you know, in home versus restaurant to help make that distinction so that people who read this and look at this information aren't mislead thinking that that, you know, covers all categories of ground beef sandwiches.

DR. BENDER: Thank you very much.

CHAIRPERSON WACHSMUTH: Okay. Art.

DR. LIANG: I think it is correct that color is not a precise measure of doneness, but there are some data from CDC that suggest that even the gross measure of avoiding pink hamburgers showed some protective effect. So there is some efficacy from avoiding pink hamburgers.

CHAIRPERSON WACHSMUTH: Okay. Katy, did you raise your flag again or is it still up?

DR. SWANSON: No, I'm not paying attention.

CHAIRPERSON WACHSMUTH: Okay. Alison.

DR. O'BRIEN: Yes. I'd like to revisit one of the original issues that was brought up about the purpose of this risk assessment. I'd like to go back to that. And I'd like to back to your slide, Wes, that you were so kind as to hand out that says what is the purpose of this risk assessment? And the way it is worded, to determine the prevalence and extent of consumer exposure to foodborne Listeria monocytogenes and to assess resulting public health impact, okay, I'm having a little difficulty with that based

on the conversation you had with Roberta a little while ago about what we set out to do because if Listeria monocytogenes is very prevalent, which obviously it is, and we're going to find it on most foods we look for it on, we're going to end up discovering that it's everywhere but only certain people get sick, which we already seem to know.

So don't we want to do the opposite of turn the question around so that the foods that are associated with a bad outcome, illness in the particularly susceptible, very young, immuno-suppressed or elderly, we want to know what kind of doses are adequate to get those people sick? We want to know issues about storage. Otherwise, we're just going to be fishing and fishing, it seems to me. That's my opinion.

DR. LONG: Okay. I'll try to address that. We're trying to do a baseline risk assessment and we're trying to consider all factors. When we get the models complete, they may indicate that the uncertainty level is very great, just as you've described. And that the exposure is, in fact, ubiquitous. I don't think that anyone has ever tried to take a data intensive risk assessment structured approach to say that. I mean it's one of those things that we all sort of know and I could have missed--you know, it may have been

said before, but no one has tried to do it in the context of a risk assessment.

So it's not impossible that we may end up, well, we will end up doing what you're saying, and this afternoon, we're going to talk about what we know about those susceptible populations, and just as a little lead-in, we don't know that much that's quantitative that relates to dose. But we do intend to fully cover that in the afternoon. That is the subject of the afternoon. There are two factors, well, three factors, the food matrix effect, whether there are certain foods give you a higher likelihood of becoming ill than others, the virulence and the relative virulence of the different strains and serotypes, and how those affect the likelihood of becoming ill, and the host factors which are critical, and so we have an epidemiological record that points towards each of these areas. But when we try to go and become quantitative and try to look at those doses that cause illness in different populations, we start to find out that there's not a whole lot of information out there to support doing that in a quantitative fashion.

But we will be getting to those issues all this afternoon and I think that while I wouldn't want to say that this part of the process is going to become irrelevant, I

think it's very important to have this baseline information across the board.

DR. MORALES: I'd like to follow up a little bit on Alison's questions and comments. Earlier the question was posed to one of the folks on the panel about whether or not you were able to assess from the literature what the link is between total Listeria and Listeria monocytogenes, and I got the impression that that link was not really clearly established yet.

In following up on Alison's question and the purpose of the risk assessment, which is to determine the prevalence and extent of consumer exposure to foodborne Listeria monocytogenes, how do you propose to use the data that reflects total Listeria and make that link between total Listeria and Listeria monocytogenes in assessing exposure?

DR. CARRINGTON: I mean I can talk about it from a modeling point of view, which--I mean actually when I put this together I was under the impression that all the numbers that are given were Listeria monocytogenes and if it's not we ought to correct for that. Okay. They are. Okay. So I think we've just included LM in our models so--I mean we could possibly include other data by if we had some correction factor for mono as a percentage of total, but so

far we haven't developed that and I don't, you know, I guess that wasn't the road we were thinking of going down.

DR. HITCHINS: Just to add to what Clark said, he hasn't been given any Listeria, total Listeria, data. He's been given monocytogenes data which keeps him quite busy at the moment.

CHAIRPERSON WACHSMUTH: I'll repeat what I heard from Dr. Hitchins' talk. In his conclusion, he talked about ways to fill important data gaps. One of those was to see if there was a way to convert species to monocytogenes. Another was to see if you could use data from one food and apply it to a related food. And a third was to see if there was a possibility of using presence/absence data. And I thought of those as potentials, not things that were being done. Is that correct?

DR. HITCHINS: Basically they're suggestions or questions to the committee to comment on or make further suggestions and additional suggestions. So we're very interested to hear the points that are being raised.

CHAIRPERSON WACHSMUTH: We have heard some concern about using species as a surrogate at this point. Nancy.

DR. NAGLE: I think we're trying to get at the question because we're all confused here. We're trying to figure out what data really is in the model or in the set

because we hear different things, that we're using general data. The question we just asked ourselves now is in that density data where you had the numbers of samples, was that only monocytogenes or was that--

DR. HITCHINS: Correct.

DR. NAGLE: Okay.

CHAIRPERSON WACHSMUTH: I think I also understood from Dr. Hitchins that he was trying to present all the data, which included data they were going to use and data that they couldn't use. And to give you that kind of transparency.

DR. HITCHINS: Correct.

CHAIRPERSON WACHSMUTH: Okay. If there are no other--Bill.

DR. SPERBER: Since you focused our attention on this topic, I'd make one comment on possible surrogates for your data gaps. I would agree with the other commenters so far that it's probably not wise to use Listeria species to estimate numbers of LM that are present. Similarly, I don't see how you could constructively use presence or absence data since I would think an important component of your risk assessment is going to be the numbers of LM and you can't get that from presence/absence data.

But your middle point on the use of data from related food types might be very useful for you. If you know enough about the foods, if you know the basic chemical structure, fat, protein ratios, that sort of thing, if you know the pH, the water activity and the storage temperature, you could very easily extrapolate from one food type to another, because they have a good idea of what will happen, in the food for which you don't have a lot of quantitative data.

CHAIRPERSON WACHSMUTH: Thank you. John and then Mike.

DR. KVENBERG: We got on to an issue I guess because of a question about the usefulness of surrogates, but I guess I would point out before just basically considering nothing valid but information strictly on Listeria monocytogenes, maybe some consideration ought to be given into how you could do a correlation or figure the uncertainties or whatever needs to be done with the data because I think a large preponderance of data information available on food subsets specifically developed by industry does not go to species. And if it can't be worked, fine, if it needs to be totally discarded, that's okay, too, but I dare say the preponderance of information that is available does not go to species. Thank you.

CHAIRPERSON WACHSMUTH: Okay. Mike Doyle.

DR. DOYLE: This is Mike Doyle. Relative to Bill Sperber's point about extrapolating the data to different food groups, I'm concerned about even within food groups. For example, certain inhibitors may be added like sodium lactate or something like that within a food group that may be a potentially hazardous food group and I think that has to be considered as well.

DR. CARRINGTON: Well, every detail has its own problem. I mean if you can come up with some reason that, you know, a particular distribution isn't representative of a particular problem, but I don't think you can go past--we can't get around the context. I mean part of the problem with doing a risk, with sort of the level we're at right now is we're trying to deal with this Listeria as sort of an abstract problem, and we're talking about the food supply in sort of abstract ways, but I suspect when we get down, you know, when we get to--I think there is going to be a policy iteration after this, and at that point, you know, certain--I sort of expect all our food groupings to fall apart. That's what I have been telling them, but they don't want to hear that.

I mean I sort of expected everything is going to have to be, you know--we're going to have to redefine our

food groups according to, you know, by industry or something else, and then we're going to have to, you know, and then we'll have to go back and rethink about, you know, which data sets are the best analogs for the problem we're dealing with. So I guess I'm not all--I think the grouping is a big--I guess I sort of agree that the grouping is a big problem and I also think it's not something we can deal with right now or even without actually getting to some, you know, thinking about what policies are going to be implemented.

So I think to some extent I think the grouping is going to have to be policy driven. I guess that's what I'm getting at. And right now we're not talking about policy.

DR. LONG: I think that we would be happy to entertain information on those different food categories. You have those printed out in front of you and any specific information that you can give us about using surrogates within that category, those sorts of pieces of information would be very useful to us.

CHAIRPERSON WACHSMUTH: I think it's also important to reiterate that there will be a closer look at each of those categories after this first large assessment. This is humongous and I know I can speak from FSIS. We would want to take those data and look at it in a much more

refined way and Dan's nodding. So I think we have to look at this first cut as a first cut. Mike Robach and then Roberta.

DR. ROBACH: Well, I just really think, though, with the propensity for one size fits all regulations and policy, the points that were brought up by Bill and Mike and Bill Sveum are very important. I think, you know, the way products are processed in a facility because a lot of Listeria contamination in ready to eat foods comes from post-heat treatment contamination, those issues and those variables need to be considered as early as possible in this. Otherwise, we do drive ourselves towards a one-size-fits-all conclusion, which I think is extremely dangerous.

DR. LONG: Thank you. We accept that comment and again any data you can provide us would be helpful and we do want to be as careful as we can. We don't want to broad-brush anything that we can do in fine detail.

CHAIRPERSON WACHSMUTH: Swami and then Roberta.

DR. SWAMINATHAN: Bala Swaminathan, CDC. On the subject of using Listeria species as a surrogate for Listeria monocytogenes, a lot of my industry colleagues have pointed out why that's not a good idea and obviously it's a very complex issue, but just for completeness of information, I would like to point out that in a recent

investigation, we did find that the numbers of Listeria species that were being quantified or at least I think--yeah, the numbers of Listeria species quantified by the plant that was implicated in the outbreak did correlate or did provide a basis for assuming that there was some correlation between Listeria species prevalence in the food processing area and the subsequent outbreak. I just wanted to bring this to the attention of committee members.

CHAIRPERSON WACHSMUTH: Thank you. Roberta.

DR. MORALES: Yes. This question is based on a comment Wes had made earlier. You referred to this as a baseline--what you're getting as a baseline from this first cut on the risk assessment. Just in general to understand the direction that you're moving in order to be able to answer or get to the objective of the risk assessment, what's the next step then? Has it been to look at different food categories and how their exposure levels differ in terms of the public health impact or which direction do you go from here after establishing a baseline?

DR. WHITING: I'm not sure I got your whole question, Roberta. You're saying did we break it down by food categories or did we look at outbreaks and--

DR. MORALES: No. More than anything else, an overall, an overview of where you intend to go with this.

Wes mentioned earlier that this was going to be the baseline. This information was going to provide a baseline for the risk assessment. And I guess my question is what's next?

DR. WHITING: Well, actually what's next is not really this group's, you know, position to say what we should do next. You know we will try to put together what we've outlined today and what information this can provide both in terms of what it can and what it can't say and we will, you know, present that and then it would be up to, you know, people in policy area, FSIS and FDA, to then redirect us and tell us there are certain areas they would then like further work on. And I could see, you know, that the second questions might require a different group of risk assessors perhaps even, depending on what the particular questions were. So we threw a couple suggestions out of areas we think that might profitably be a second look, but I don't really want to prejudge at this time what it would be.

CHAIRPERSON WACHSMUTH: I can reiterate what I said a minute ago, too. At least looking at it from FSIS' point of view, we would intend to do probably a more pointed risk assessment in terms of what we might want to do in a regulatory way based on what this group presents. That was the intentional initially. Spencer.

DR. GARRETT: Spencer Garrett with the National Marine Fisheries Service. I just have kind of a scoping type clarification question, if I could. As this process proceeds, the Codex [?] Commission has passed, and many people know this, the general principles and guidelines for the conduct of microbiological risk assessment and there are 11 principles and guidelines and so forth.

But I think--and it's a very good document to follow. It pretty much is a road map, but in that one of the principles is is that the risk assessment self, you know, has four components: hazard identification, hazard characterization, exposure assessment, and then risk characterization. And I presume that as you proceed through this process in which we're engaged that these four steps or very similar categories of information will be collected. And then in the risk characterization itself, there will be some probablistic statement, if you would, characterizing the risk in some output form, meals served, or you know whatever the risk managers want.

But is that essentially the general track that this assessment is going to follow using those four steps and then having a characterizing the risk statement with an output, characterizing the risk with an output statement essentially?

DR. WHITING: Yes. I think we're following those fairly closely.

DR. GARRETT: I think you are.

DR. WHITING: I would characterize our draft charge and the presentation last spring as sort of the hazard identification steps. This morning was pretty much the exposure assessment. This afternoon will be the hazard assessment. And that's sort of where we are now and then we will attempt then to bring all those together. In terms of outputs, you know the exposure assessment we will be looking at in terms of say numbers of Listeria consumed from different food groups. And there are different ways we could break that down and express it and we will be talking to some of the risk managing group to determine exactly how they would like that expressed. And likewise, in the hazard assessment part this afternoon, we will be trying to say as much as we can about that. So, yeah, I think we're trying to follow that paradigm as closely as we can.

DR. CARRINGTON: I think there's a problem with the NAS paradigm which is it doesn't, it's portrayed as a monologue which sort of proceeds from data. You know you go from data to analysis decision, which makes the whole process look like it's data driven as opposed to being problem driven.

And the paradigm I like to show is like the NAS paradigm but it has feedback loops where not only does risk assessment feed into risk management, risk management feeds into risk assessment, which is to say--and the idea is the risk manager is basically responsible for asking the question I think is the other way to put it. And so I think, you know, following risk assessment, there's going to be a policy iteration, and then they will ask another question and I think basically sort of the way I envision anyway the question going of what we're doing now is we're sort of trying--right now we're trying to give sort of a picture of the state of the union with regard to Listeria. You know this is the way things are now and then we'll go to the risk managers and say, well, okay, what are you going to do about it.

And then they may propose some action or regulation that is intended to intervene with Listeria making people sick and then we may go back and try and figure out whether or not that's going to work or not or whether there is some reasonable expectation of it working. And so that's how I envision the process. I don't know if everybody envisions it that way, but that's my idea.

CHAIRPERSON WACHSMUTH: Spencer.

DR. GARRETT: Yes, I didn't want anyone to conclude from my remarks that I felt that something was untoward. Frankly, I want to commend the group, the team, if you would, that you are following the Codex general principles and guidelines very well, and I was making the comment to try to infer that this is a process, not an event, and there are obviously other things that are going to have to have happen, but I think this is a new day for science in this country quite frankly for--and we had a little sidebar discussion--we're getting away from some of the swag theory and now actually getting serious about doing risk assessment and, in fact, identifying the uncertainties for perhaps in some instances for the first time.

And there is a lot of uncertainty in this business, but, on the other hand, you have to make regulatory decisions on the best information available and the best information available is just that. It's the best with the uncertainties noted. Thank you.

CHAIRPERSON WACHSMUTH: Thank you. Bill.

DR. SPERBER: Thank you. This is Bill Sperber. I was encouraged by the several comments of the chair suggesting that this risk assessment procedure was a broad-based approach to the issue of Listeria monocytogenes in

foods and that it could possibly well be followed up by more specific risk assessments for particular food categories.

I agree that this is a very useful process that you're conducting and that you're off to a very good start, but I further believe that the results of your risk assessment here, the broad-based risk assessment, could well lead to some very important, far-reaching, long-lasting public health policies, and if you do continue this process to develop specific risk assessments for specific product categories, I would suggest that it's incumbent upon the risk assessors in those cases to get their own data on which to base their risk assessment rather than having the risk assessment rest strictly on literature data.

I think at a minimum you would need to collect enough data to validate the model that you generate from your risk assessment.

DR. CARRINGTON: Well, how are we going to get data? I mean with us and what army? I mean--

DR. SPERBER: How will you get the data?

DR. CARRINGTON: Right.

DR. SPERBER: Well, you have vast resources, vast laboratory resources--

DR. CARRINGTON: No, we don't.

DR. SPERBER: --at your disposal.

DR. CARRINGTON: No, we don't.

DR. SPERBER: The government does. Somehow. FSIS, for example, is doing a lot of survey data on other pathogens so perhaps it could be arranged that you could at least have your own government laboratories do enough surveillance to validate your models.

CHAIRPERSON WACHSMUTH: Dr. Potter.

DR. POTTER: I think if we go back to one of Wes' earlier slides, you pointed to this risk assessment being conducted within a larger context of work being done on Listeria, that should help to refine some of the data. Obviously, if we had already in hand the kind of data that Bill referred to earlier that would help us distinguish between various categories of lunch meat, we could make this first cut more refined.

But I think that over the next couple of years, government laboratories and epidemiologic research will, in fact, help us refine the model to a considerable extent. So it's a good point, Bill, and I think that validating the model is in the cards, but as Clark implied, it's a fair piece of work and will take some time to get done.

CHAIRPERSON WACHSMUTH: In fact, I think it's fairly common knowledge and I'm sorry that Dane is not with us today, the government through one of the USDA agencies

has awarded a grant to NFPA to do survey of broad, I mean--broad-based--my favorite word today--but covering a lot of other, a whole spectrum of products over a two-year period. This is not something that will be done quickly. But as information becomes available, it's my understanding that this will fit into a model that's being designed at this point. Clark, didn't mean to cut you off.

DR. CARRINGTON: I was just also going to say something. I don't even think it's meaningful to talk about validating the model because, you know, we have no expectation that the model is going to survive experimentation. I mean if we get more data, the model is going to change. I mean there is just no doubt. Like a lot of parts of the model are really simple and the reason they're simple is because we don't have any data. And the minute we get some data, we're going to want to change the model. So it doesn't--I think we can develop more accurate models, but models are never any better than the data and a lot of times what we just need is more data.

DR. LONG: I think I want to make a comment about the cart and the horse. I think that what I'm hearing is that we should have the data before we do the risk assessment and I think what we're saying is you've got to do the risk assessment to figure out what data you need and I

think that I can stand behind that second statement because of the fact that we're trying to do a risk assessment and we're looking for the data and we're having a hard time finding it.

So I think that the risk assessment drives identification of the data gaps which will drive the government research agenda and drive the research agenda of affected parties.

CHAIRPERSON WACHSMUTH: Art.

DR. LIANG: Yes. That's actually why I asked my question about of the 15 or so boxes, if you'd had enough experience yet, you know, cranking in some data to try to identify the most important gaps that you have and ask this audience whether we have some of it.

CHAIRPERSON WACHSMUTH: Okay. Any other? Dick?

DR. WHITING: Yeah. I got to throw a question back to our committee here that kind of summarizes this section as I see it, and that is we have a tremendous amount of presence and absence data. But when it comes to quantitative data, even though Tony showed some fairly high numbers, would it be fair to say to Tony and Mary there are some food classes there which we really do not have any quantitative data on Listeria? And even in some of the other food groups, the amount of quantitative data is really

rather scarce. You can bounce off that a little bit more in detail, but I don't want to leave the impression with people here that we really have got a lot of data that we can work with and we can begin to split these categories up into fine pieces and so on because the amount that has been collected, whether it's university or certainly within government, it is really very little relatively speaking that's quantitative.

And that then is what was driving the question that Bill Sperber partly addressed here when he said what can we do with all of this presence/absence data that is available? Is there any way that we could take that data and begin to use it? So I don't know. Tony, do you want to agree or elaborate?

DR. HITCHINS: Which part of your--use of presence and absence data? Yeah. Well, some of the presence and absence data has not been used although there is corresponding to it the enumerative data and so I can pass that on to Clark if he so wishes and he can incorporate that presence and absence data into his general model. It will increase the number of points, if you like, at the point which he has on his graphs where the detection limit of the methods are located and so he will--and he can correct me on this; I'm sure he will--have a stronger anchoring of that

curve at its lower end of available data. So some of the presence/absence data is usable in that way.

In other cases, we may have presence and absence data which is not matched by some quantitative data. In that case, you could only use that kind of data by making assumptions about what I would call the standard deviation of the distribution curve, although that's not an appropriate word because there are different kinds of distribution curves that Clark is dealing with, but one could make some assumptions about using that kind of data that way. That is you really--presence and absence data gives you one point or one cut on the distribution curve and by plugging in some correction factor, you could estimate a second point and therefore get a distribution curve.

DR. WHITING: Tony just kind of outlined it two ways you might possibly use data when there is no quantitative. You know do we just assume that if it's two percent positive, just put in the value of the detectable limit and go ahead and put that in? Now that's probably greatly overestimating, but then again you have no idea in that say two percent positive what small fraction of that was really very high numbers. But, again, putting that in is one way to try to put data in.

Or the other, as Tony said, you create a distribution where you have quantitative data and then try to, say, take that distribution and the standard deviation and say if it's two percent positive, what do we think that tail looked like? Or if it's five percent positive, what do we think that tail looked like? And I just would like to throw this question out to the committee if anybody has any particular opinions on how they think we should handle some of this data or whether we can at all.

CHAIRPERSON WACHSMUTH: Swami.

DR. SWAMINATHAN: Bala Swaminathan, CDC. I think from the data presented this morning by Dr. Hitchins for soft cheeses, 88 percent of the 2,232 samples, they're really in the range of less than 0.04 cfu per gram. You know one way to use the qualitative data will be when it's absent, you know that it's less than 1 cfu per gram and then it's .04, whatever you did the calculations this morning. And to take a positive as greater than .04, that's not entirely satisfactory, but we do expect low numbers in most foods that we test. So this may be one way of handling that situation.

DR. HITCHINS: Well, that's essentially what we've been doing. Yeah. In some cases at least.

CHAIRPERSON WACHSMUTH: Okay. I think we have no registered presenters for public comment at this time. So that will give us another almost ten minutes for lunch. I think we should stay on schedule and be back here at one o'clock. Thank you, everyone, panelists, in particular.

[Whereupon, at 11:45 a.m., the committee recessed, to reconvene at 1:05 p.m., this same day.]

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

[1:05 p.m.]

HAZARD ASSESSMENT

CHAIRPERSON WACHSMUTH: Okay. I think we better get started so we can finish before supper. Just a little more information on the December meeting. We've had time now to consult with the risk assessors and others, and we should be able to meet the 8th, 9th and 10th. But we would have the juice meeting first on the 8th and the 9th, and then we would have the 157 risk assessment on the 10th.

The team, the 157:H7 team, is presenting their models, their draft assessment at the Society for Risk Assessment on the 8th. So what they're going to do is just bring those presentations to this committee on the 10th, and I've heard at least part of what they're going to say and I think you'll find it interesting.

PARTICIPANT: Where is the meeting?

CHAIRPERSON WACHSMUTH: It will be in D.C. area. I'm not sure that we have a hotel yet. Do you know? We may be here where we are right now. Okay. I was trying to stall for Morrie a little bit, but I think that we should go ahead and start. He has heard the presentations at one point. So, all right, Dick, do you want to start us?

DR. WHITING: I'll introduce our people. Okay. I should also mention here we have been sending handouts around of the slides that are presented and if you haven't gotten them I think they're outside. I would like to caution you, though, of course, this, the slides here--this is our working presentation, if you will. This is where we are at the moment, and we won't stand by any of that in December.

[Laughter.]

DR. WHITING: Okay. Having said that, this afternoon we're going to be focusing on the other half of the risk assessment, the hazard or dose response part of it. And I'd like to just to introduce our three speakers and I think we'll follow essentially the same format we did this morning where we can have perhaps a few questions after each speaker but we then plan to have a general discussion with all of them afterwards.

The first speaker will be Dr. Pat McCarthy, who will review the epidemiological information. The second is Dr. Richard Raybourne who will look at some of the more formal dose-response studies from animal and other data. And then Dr. Clark Carrington to describe how this will then fit into the modeling context.

And I might just ask again, you know, this is a section where we have some fairly major concerns, questions within our group, of just how we should handle some of this data, so we are going to be very interested in hearing back from you and the panel of what you think and what you think we should do for this section. So, Pat, do you want to begin?

DR. McCARTHY: Good afternoon. I'm going to talk about the Listeria monocytogenes human hazard assessment. Listeriosis is the group of disorders caused by Listeria monocytogenes. The clinical definition or the clinical listeriosis is defined when Listeria monocytogenes is isolated from a normally sterile site like the blood, spinal fluid, fetus or placenta.

Surveillance has been conducted for Listeria dating back to 1989, and from 1989 to 1993, the incidence of Listeria has decreased. In 1989, it was approximately eight cases per million, and in 1993, it dropped to about four and a half cases per million. FoodNet data from 1996 through 1998 indicate that the rate has stayed approximately the same at about five cases per million.

Now, five cases per million is not a lot of cases, but when people get listeriosis, quite a few of them go to the hospital and--this is more FoodNet data--compared to

other pathogens tracked by FoodNet, listeriosis will put more people into the hospital than the other pathogens.

Listeriosis has severe symptoms. The most severe symptom commonly encountered is sepsis. There is also meningitis and death and you can see some other rather severe symptoms. In terms of the population at risk, we've estimated that the population at risk is approximately 20 percent of the U.S. population. This includes pregnant females and their fetus, the neonate, the elderly, and the immuno-compromised. And I've given some examples there of what I mean by the immuno-compromised population.

There is a form of listeriosis that seems to--you see in pregnancy. The maternal cases will often present with a flu-like illness and some of those will develop a sepsis. The fetus and neonate--in the fetus, you will see abortion or stillbirth as a possible outcome. In the neonate, you can have meningitis, sepsis or the neonate can die.

There are two groups that are predominantly affected by listeriosis and that's the very young and the very old. Those 50 and above, the 60 and above, that elderly group also includes quite a few of the immuno-compromised. There's a mild form of illness associated with Listeria. These are predominantly GI symptoms. You'll get

diarrhea, vomiting, nausea, but you'll also get some muscle aches, chills and so forth.

The incubation period for Listeria, listeriosis, varies quite a bit. It goes from less than one day to there's been reports of up to three months. The severe illness, you'll see the incubation period usually will be from days to months, and in the mild illness, it will usually be from hours to days.

There is reports--there are several reports of fecal carriage of the Listeria organism. In the human, the GI tract is the resident place for the organism. It's been estimated in various populations that fecal carriage in the population ranges between one percent to 21 percent. It's not known how the fecal carriage rate relates to the link of incubation or to the occurrence of illness. It's been suggested that stress can possibly undermine resistance and lead to an illness.

I looked at the literature, the epidemiologic literature, on outbreaks and sporadic cases and I looked at surveillance. And when I was evaluating the studies for this quantitative risk assessment, I considered the items that are here. I wanted to be here that there was a strong positive association first, that I was looking at studies about Listeria and not about some other pathogen. I wanted

to be sure that cases in controls were treated the same. I'm not talking about being treated in the medical sense, but that they were interviewed in the same way and that they were given the same questionnaires.

And that all factors related to the outbreak were considered. Specifically, I was looking for reports where the exposure was quantitated and linked to individuals. And now I'm going to show you some of the studies I found where we had dose information. Let me just say at this point if anybody knows of any other study where there's dose, there's an attack rate, and the number ill is reported in the article described in the outbreak or the sporadic case, please let me know.

There was an outbreak in 1985 in Los Angeles that involved some cheese. Most of the serotypes were LM 4b. It was estimated that the contamination in the cheese ranged from 14,000 to 50,000 colony forming units per gram. There were approximately 142 persons that were involved in the case control study, but actually there could have been as many as another 160 people that were affected during this outbreak.

We don't know the amount consumed and we don't know the attack rate. This is a real problem and you're going to see, as I go through these studies, that something

is missing. For the most part in all these studies I do have the dose listed, but the amount consumed and the attack rate are problems.

There was an outbreak in Switzerland. It lasted for about four years. It also involved cheese. About 75 percent of the isolates were LM 4b. Contamination in the cheese was estimated to be to range between 10,000 and one million organisms colony forming units per gram. Again, we don't have the amount consumed. The number ill over this four year period in western Switzerland was approximately 122, but we don't have the attack rate.

There was a chocolate milk outbreak in the midwest in 1994. The serotype here was LM 1/2b. The concentration of pathogen of 1/2b in the chocolate milk was estimated to be approximately one billion colony forming units for a milliliter and the amount consumed in this case--this might be the only study that I have where they've estimated the amount consumed--the median amount consumed was one carton of milk. It's hard for me to imagine that actually one carton of milk might have been consumed if it had one billion colony forming units per milliliter. I can imagine that most people took one sip and that was it, but it was reported that it was a median consumption of one carton of milk.

In this outbreak, approximately 90 people or so attended the fair. 60 of those consumed milk, consumed the chocolate milk, and 45 of those got ill. So we do have an attack rate here. This is an odd study in that the contamination is so gross. Also, in the paper that reported this study, they did talk about some surveillance that was conducted in the three months around the time of the outbreak. And it was in some states that are out in the midwest. During the three month surveillance, they identified 27 isolates. They collected 27 isolates. Nine of those isolates were sent to CDC for serotyping and three of those isolates were identified as the outbreak strain.

Now, in these three people that they identified as listeriosis cases with LM 1/2b, those folks had sepsis. They purchased milk from--the milk could be traced back to the implicated dairy, but possibly that milk was not treated or abused in the same way that the milk at the outbreak. So we don't know the contamination level or the consumption level for those people that were identified in the surveillance, but this is a study--this is probably the only study that we have that does have all the pieces of information and we're deciding how to use this.

This is an outbreak that took place in Italy. This was a private party and at the party several foods were

served. You can see here that they identified an LM 1/2b in four, four different foods, in shrimp, in cream cheese and in a fruit tart. And I do have the contamination levels. The rice salad was eventually epidemiologically implicated as the source food in the outbreak, but by the time they got to analyze the rice salad, it was gone. There was none left.

So even though the rice salad was epidemiologically implicated, it was never shown conclusively that it contained the serotype in the outbreak. We don't know the contamination level in it. We don't know the amount consumed, but in this case we do have the number ill and we do have an attack rate.

This is an outbreak that occurred recently in Finland. It involves butter. This is the serotype that was implicated here was an LM 3a. This is the first time that I've come across 3a in reports that had dose related to it. The contamination level here was estimated to be less than 100 colony forming units in most of the samples that were analyzed, but there was one sample that had about 11,000 colony forming units in it.

The amount consumed is not known. The number ill, I've just gotten, I've just had some correspondence with the researcher and it's been placed at 24 at this point. That

could increase or decrease, but we don't know the attack rate.

Another recent outbreak was a multi-state outbreak involving some hot dogs. The serotype here was LM 4b. The contamination level in the hot dog was estimated to be less than .3 colony forming units per gram. We don't know the amount consumed here. At this point, the number ill has been estimated to be 101 and we don't have the attack rate.

Now, this is a busy slide and the intention of the slide is not for you to read it but for you to see that in all these outbreaks here, the number ill is either one or two. The amount consumed is not stated in most of these. In three, in two of them we do have an estimate of the amount consumed, and then one we have a vague estimate of the amount consumed.

The attack rates are one cases. Our modeler is thinking about this data. We're trying to decide what to do with it, but again we don't have the amount consumed. We don't have a dose and the attack rate is one person. Of course, the attack rates could be more, but the literature that I reviewed didn't give me any additional information.

So, in summary, throughout my review, I've assumed that human data where exposure is quantified and linked to individuals is necessary for a Listeria dose-response model.

The limitation that I found is that few human epi-studies are available that meet the requirements for a quantitative risk assessment.

I conclude that human epi-studies provide limited information for Listeria dose-response modeling. Let me just say this again that if anyone knows of additional studies where there is a dose, there is an attack rate, and number ill, if you would share that information with me, I'd certainly appreciate it. And that's it.

CHAIRPERSON WACHSMUTH: Thank you, Pat. Questions for clarification right now and discussion later. Mike.

DR. DOYLE: This is Mike Doyle. If you conclude that there is limited information available, are you going to use that information?

DR. McCARTHY: We're going to use every bit of information that we can. It's just hard to use information that has so many gaps.

DR. DOYLE: I would agree with that. I would be real concerned about using some of those data where you really don't know how many Listeria were in the food which the individual who became ill actually consumed.

DR. McCARTHY: Correct.

DR. DOYLE: The hot dogs, for example, that was a shelf-live study sample, as I recall, that was tested and that wasn't what people were directly exposed to.

DR. McCARTHY: That's correct.

DR. DOYLE: That might be a stretch.

DR. McCARTHY: Thank you.

CHAIRPERSON WACHSMUTH: Okay.

DR. McCARTHY: Thank you very much.

CHAIRPERSON WACHSMUTH: Very nice. Thank you, Pat. Rich, you want to talk to us about your part of the hazard assessment?

DR. RAYBOURNE: I'm going to talk about the hazard characterization portion, the more, I guess, the more dose-response related information that we were able to obtain. It has my name up there, but I was also helped a lot by Dr. Tina Ralph and also by Dr. Wes Long in developing this presentation and the data that goes into it.

In addition to the overarching goal of doing the hazard characterization, the kind of specific goal that we had started out with was basically to develop a data driven, quantitative approach to dose-response modeling. As you've heard from other speakers, one obstacle to achieving that goal has been the sort of lack of all the data that you might necessarily want to have to accomplish this goal. But

at this point, I'd also like to say that during this process, we have gotten data from a variety of investigators, from--several investigators have offered data, some of it unpublished or most of it unpublished, as of yet from their laboratories pertinent to our efforts, and we'd like to thank them for that. And not all of it has been incorporated in this presentation, but we plan to ultimately use whatever of that data we can use.

The resources for this--Pat has already talked about the human, basically the human data, the epidemiology and the case report data that he has gone over. I'm going to focus on surrogate data sources. That is animal studies and--well, actually what I'm going to talk about is actually all animal studies. Another possible source of surrogate information in terms of dose-response is in vitro studies and in vitro model systems as well, but they actually have not figured in at this point to what we're doing.

Looking at the various parameters of dose response, we focused in on three: the effect of food matrix on infection; the effect of pathogen virulence; and the effect of host susceptibility, all sort of working together to produce a variety of outcomes which Pat has also talked about all the way from a mild form of listeriosis to the more severe fatal forms of the disease as well.

In general, the approach that we've taken is to use experimental animal virulence studies to define or determine a range of relative Listeria virulence. In terms of susceptibility, we've also used animal models of immuno-compromised states to focus on the information available as to the relative susceptibility of different types of compromise populations.

As we proceed through this effort, one of the things that we're concerned with is that wherever possible, we look back at the human epidemiology case report data to see if the answers we're getting are sort of making any sense to the situation as it exists on the ground, so to speak.

For example, this could also be interpreted to mean that we don't necessarily think that the absolute numbers that we're going to derive from the animal studies are going to turn out to be directly extrapolatable to the human situation, but we may develop some information regarding ranges of virulence and ranges of susceptibility that may be then linked to the human situation.

Talking first about food matrix, we actually have relatively little information on food matrix. The concept of it would be that Listeria monocytogenes in an acid or high salt environment may, this may increase its ability to

survive in the stomach acid barrier by essentially turning on adaptive mechanisms in the bacteria so that it's then allowed to survive under sort of related conditions of stress that it might encounter and thus enabling it to survive more effectively.

The other idea is that there could be a role of high fat content in foods which may protect LM from gastric acid or enhance uptake and survival in host cells through some interaction between the lipids in the food and the lipids in host cell membranes. Unfortunately, I wasn't actually able to find any quantitative animal information on this or dose information on this aspect, which comes through. In the next slide, we have basically no conclusions on food matrix at this point.

We are still holding open the assumption that food matrix plays a role and may play a role in dose-response. And the limitations are that we have not found at this point or been able to incorporate a lot of quantitative animal studies looking at this issue.

Moving on to pathogen virulence and its role in the dose-response relationship, there's a considerable bit of evidence based on epidemiology in case reports for variability in virulence of Listeria. For example, most human cases are associated with a restricted number of

predominant serotypes. Those particular numbers were gleaned from a review article by Farber and Peterken [?], but I think other numbers seem to be similar. Those are sort of worldwide numbers.

Also, the technique of ribotyping has also been used to identify disease associated subtypes in Listeria and at least in one scheme has been grouped into three lineages or families of Listeria with lineage one being associated with most of the human outbreaks and lineage three basically being associated with almost none of the or with no human disease.

In addition to that, the relationship that suggests the variability is the fact that even though most of these ribotypes or there are certain associations between subtypes of Listeria and disease, these associations don't parallel the frequency of these serotypes or subtypes as they're found in food. So it's not simply a question of being--it suggests that there are some qualitative difference between these strains of Listeria.

In addition, we've also been able to find animal studies which show a range of virulence among food isolates of Listeria, which we will look at in a minute.

Another piece of evidence that has cropped up fairly recently in terms of evidence for variability comes

from the recent outbreak of listeriosis associated with hot dogs. And it turns out that, of course, as most of you know that these hot dogs were actually--there is evidence that they were actually contaminated with more than one strain. They were contaminated with two strains of Listeria, one of which was a serotype 4b and the other was a 1/2a.

The outbreak illness was associated only with the 4b and the ability to produce the illness on the part of these strains was not correlated to the cfus per gram. That is the half-a strain which produced no human illness and was never--or at least was never isolated from a case of human illness, was present in much higher numbers in that particular case, suggesting again that all Listeria are not --Listeria monocytogenes are not exactly the same.

Looking at some animal virulence studies, this is a study looking at a variety of Listeria strains from various food sources and in addition a couple of clinical strains as well. Looking at LD-50 dosage in mice, these are carrageenan [?] treated mice which are therefore an immuno-compromised sort of model, and you can see there is a range of roughly three logs among the food isolates of Listeria in terms of their LD-50s. A couple of other points that are interesting to me on this slide is that the two clinical isolates, Scot A and I don't know this other clinical

isolate here, were not markedly different than any of the normal food isolates.

In terms of serotypes, actually all of the food isolates were serotype one and Scot A is the only 4b in this study. So these kind of impact on what comes later in the talk. The other interesting point is that a non-hemolytic mutant of another strain of Listeria shows, of course, a massively lower rate of infectivity even in the compromised animal model.

Here's another study that is somewhat similar and I bring this up only to point out this because this deals with LD 50s in normal versus compromised animals although it has fewer strains involved in it, and again pretty much the same sort of range of virulence actually or range of LD 50s crops up again in the normal animal as well. These non-pathogenic strains all have much higher levels of dosage required to reach the LD 50. Scot A is in this study as well, and it's again not markedly different than the food--I don't know the serotypes of the isolates in this one except, of course, Scot A.

So basically, the conclusions that we've reached are that a range of virulence does exist. We are also making the assumption that the animal data which we found and any other animal data which other people may know about

can be used to characterize this variation in Listeria virulence.

I'd like to discuss briefly some of the limitations on these studies which I've sort of already alluded to. First of all is that the serotype, phagetype, ribotype data are primarily used or developed as epidemiologic tools to identify these organisms in sort of a trace back mode. But those characteristics as subtypes are not necessarily or not mechanistically related to any of the virulence mechanisms of Listeria such as the presence of the hemols [?] and the presence of internalins or the presence of the Act and polymerizing protein ActA.

Secondly, the predominance of these certain serotypes identified in the outbreaks may not actually even be related to any of these defined virulence factors. It may have nothing to do whatever with virulence factors and be related to other properties if the organisms such as ability to colonize certain foods, ability to withstand gastric acidity. It may not really--or there may be other undefined virulence factors that we're not aware of yet that are present in these strains.

Finally, we were not able to find any animal or in vitro studies that were directly correlated to any of these subtypes with virulence measures. If you look at these

strains in vitro virulence assays, the differences between them in looking at things such as the ability to invade certain kinds of cell lines is really not correlated or remarkable in studies that we have observed. So we're going to look at some of the data. No, we're not. We're going to talk some more limitations.

Secondly, in addition, besides the point that there is a strong association between certain serotypes and ribotypes with human disease, it's also true that all serotypes have been associated with at least some human illness at some point in time.

Secondly, in this slide, if one were to try to take a kind of a genetic approach at characterizing virulence, it would, of L. monocytogenes, it would be probably an exercise in futility because basically all food isolates contain the genes for the major virulence proteins of Listeria monocytogenes. And thirdly, the in vitro and the animal studies are inconsistent in showing a pattern of virulence among food isolates versus clinical isolates. That is the point with, for example, with Scot A or other clinical isolates in these in vitro and animal studies don't stand out as being more virulent than other Listeria isolates that have not necessarily been associated with causing any disease.

So there are some problems with that area. Finally, looking at the area of host susceptibility, as a third sort of side in this disease, not triangle, there is some, again, some evidence for susceptibility based on real life case reports. First of all is the observation that Pat discussed that healthy adults are usually asymptomatic after exposure and that there are a variety--that most disease cases are associated with a variety of predisposing conditions, at least some of which have to do with the immunological status of the host although not all of them. For example, one could say reduction in gastric acidity might be a predisposing condition which may not have--which is not associated with immunological factors necessarily.

So the overall approach then taken for dealing with the susceptibility issue is the proposition that among the susceptible human populations, we could identify bio markers of susceptibility. Some examples would be, for example, in the case of HIV infected/AIDS, individuals with AIDS, the most obvious thing, of course, is the absence of the CD4-T cell population. This is actually a little bit problematic in a way because in some animal studies, it's known that the role of CD4-T cells occurs much later following infection than--and is related to the induction of a kind of sterile immunity to the organism rather than

control of the organism following the initial infection. And on some animal models such as nude mice which lack CD4-T cells and Skids mice which also lack actually any T cells, there's actually a surprising resistance to Listeria.

So there may be other things going on in these HIV patients that are under therapy, various kinds of therapy that may be influencing what goes on with Listeria. So it may not be as simple as the CD4-T cells actually. But in terms of the elderly and infants, they are known to possess a variety of alterations in both the innate and acquired immune systems, arms of the immune system.

For example, there are changes in the ratio of memory to naive T cells associated with these populations. In terms of pregnancy, the findings are also quite interesting and suggestive. For example, during pregnancy, there is actually an inhibition of the NK, of the natural killer cells in the placenta mediated by the presence of a non-polymorphic HLA antigen that down regulates NK cells in the placenta.

That's important because in most mouse models or in mouse models, it's well known that the natural production of gamma interferon by natural killer cells is extremely important in the early phases of resistance to Listeria.

Secondly, during pregnancy, there is a shift to a so-called Th-2 cytokine environment. The reason for this, of course, is to inhibit the negative effects of the Th-1 type cytokine profile and T-cells acting on the fetus. The same is true actually of the NK cells as well that I just mentioned. And this then relates to Listeria because it's well known that Listeria--resistance to Listeria is again dependent on a Th-1, that is gamma interferon interlukin-2 type cytokine environment.

If you'll look at some measurable parameters related to susceptibility in humans, you can see that some pieces begin to fall into place. For example, looking at the ability of the young versus elderly T cells to produce gamma interferon. You can see there is roughly about a maximal tenfold difference. Similarly, looking at the interlukin-2 receptor levels actually in blood, you can see again a proximate tenfold difference.

Interestingly, the IL-4 and the IL-10 response are exactly the opposite. That is they're enhanced in elderly patients but this, too, correlates with the animal model because it's known in animal models that IL-4 and IL-10 actually can serve to exacerbate some phases of Listeria infection.

Finally, the last three parameters are parameters related to innate components of immunity which show actually to a lesser degree a kind of inhibition in elderly patients. So we felt that we would take the approach that the host resistance mechanisms targeted in animal studies which we would use to look at susceptibility would be connected with human biomarkers of exposure and susceptibility.

Of course, there are some problems with this approach. First of all, the compromised animals in some studies that we found were not always identified with specific immune mechanisms. The method used to compromise the animals might not necessarily have a particular defined effect and could be more of a sort of a broad-stroke sort of approach. The very specific models, that is the knockout mouse models where genes, specific genes are deleted related to resistance also represent a kind of a worst case scenario for susceptibility in the sense that they're, you know, basically or probably not humans that are the equivalent or at least not very many of them that represent the equivalent of a animal with a completely missing component of their immune system, particularly in terms of the cytokine type responses. So that these kind of studies could perhaps be used as a kind of upper bound for the effect of

susceptibility although not necessarily capturing a range of susceptibility.

Thirdly, many of these animal models have not been tried with oral dosing studies. Mostly these studies involve parenteral inoculation of Listeria and therefore we don't really know how the phase of the disease which involves invasion of the gut epithelium and getting into the circulation is affected in these models without doing oral dosing type format in those experiments.

Finally, the experimental design and the data format may not really be suitable for doing the kind of dose-response modeling. The studies that we looked at were for the most part not done for the purpose of doing dose-response studies. They were done for the purpose of identifying mechanisms of resistance. So oftentimes in those studies, there simply are not multiple doses used. Not to criticize the studies, but simply to say that it was not the intention of the people doing them to look at this issue.

For example, looking at some of these kinds of studies where you have an inhibition of interluken-6, interluken-12, TNF alpha, gamma interferon, and interluken-1 in for the most part knock out models, the data shows pretty dramatic effects actually. You can see that these things

are definitely important in resistance. However, actually only one dose was used in these studies and the result was produced by simply comparing the rate of death in the control versus the animal model. Also, similarly, some of these studies, the data is expressed only in terms of colony forming units in spleen or liver for the two, for the control and the compromise model.

There are some studies, however, where people do do dose-response work. Here's one particularly where using a neutrophil depletion model, that is a model which knocks out a component of innate immunity, very important component for Listeria, and this study is also interesting because it was done with, it was done with an oral dosing model, and we were able to use this model or at least this data to help model some level of susceptibility.

In addition to the sort of very specific models, it's been known for quite a long time, since the '70s, that certain mouse strains are more susceptible or resistant to Listeria, and there was dose-response data actually in addition to this, but I'm just showing this particular study, using the susceptible AJ mouse strain versus the more resistant C-57 black 10 strain, to model this so that you could look at a difference between these two strains.

It turns out that, you know, a bit more is known about this than I've alluded to, that the defect in these animals is actually related to a macrophage defect or a macrophage characteristic in the susceptible strain so it, too, is related to some specific definable immune cell defect.

Finally, we have another study here which was used in which the C-57 black model was treated with a high dose steroid and producing a fairly dramatic effect in dose response in both LD-50 and ID-50, and this study has the advantage also of sort of comparing how LD-50 and ID-50 relate to each other as well, which is important because those kind of endpoints are actually used in other kinds of studies as well, and that enables you to kind of link what they mean to each other, I think.

Finally, to get away from everything immunological, there is a model of looking at gastric acidity in which animals were treated with cimetidine or control animals and was used or could be used to develop a model of the effect of gastric, decreased gastric acidity on Listeria infectivity.

So, in conclusion, our conclusions are that animal dose-response data can be used to establish distributions for relative pathogen host susceptibility, highlight the

"relative" pathogen host susceptibility. The assumptions we're making are that the human and the animal resistance mechanisms are similar. The limitations primarily are that the available experimental data tends to reflect extreme immunological scenarios, for example, complete depletion of a component of the immune system. And that's the end. Thank you.

CHAIRPERSON WACHSMUTH: Thank you, Rich. That was very nice. Clarification questions? Okay. We have a modeling talk, Clark.

DR. CARRINGTON: All right. I'll start with this slide again. Now I'm going to pick up with Listeria per meal and I'm going to go down and proceed on through all these boxes until I get to number of cases, and I guess probably the central part I'll talk about just how everything fits together. Let me talk about this dose frequency function here first because this is a little different than the rest of it.

Most of this model is modeling sort of at a meal level so you're tracking a meal from how much Listeria it has and then we're going to get to the box before the dose-frequency function at that per capita meals per gross group. We're going to condense all that information into the number of meals at a series of dose groups. We'll probably have,

say, 20 dose groups at half-log intervals going from zero to 10 to the 10th Listeria. And then that will plug into this dose frequency modeling function and that will predict the total number of cases.

All right. So but in between actual number of Listeria per meal and at dose frequency model, there are some adjustments that are going to be made to the actual number of Listeria to make them match the derivation of the dose-response model, which--and the three main ones here are going to correct for or account for strain virulence, differences in host susceptibility, and differences between the rodent data from which the dose-response models are derived and humans.

First of all, the strain virulence data pretty much Rich showed. I'm basing--I have a distribution I developed from the 14 strain study, which you already saw. The one modification I'm making is I'm converting--first, I'm converting them all to logs, and I guess that's the common theme for all three of these modifications is they are all based on log adjustments in the dose so that the actual number of Listeria in the sample are pushed one way or the other by some modifying factor, which is generally distribution which varies in the meals as consumed.

So I guess the reason this is dose-response is not just the meal, it's also who's eating it that matters. Okay. So the who's eating it, you know, and furthermore what the strain in the meal are, actually is.

So in addition to taking the log, I also standardized everything on Scott A, which--and just to show how I did that, basically the LD-50 in this study for Scott A, the log 10 of the LD-50 was 1.97, so I subtracted 1.97 for everything. And I picked Scott A because it was in the middle of its distribution. It's a clinical isolate and it's also fairly commonly studied. But for the purposes of the risk assessment, it wouldn't matter what standard I picked since everything is relative to everything else.

Okay. Then I fit five different models to this distribution and that's what they look like. The ones that fit the distribution a little better are given a little more weight than the other ones, but nonetheless these five models I'm using to represent the uncertainty associated with this distribution.

And next problem. For host variability, probably this is the least well developed of any of these that we've worked on--I mean actually we've sort of been arguing about this more in the last week than we have in the previous or discussing this more in the last week than we have in the

previous several months. But I guess the main point, the main thing I think we can get out of the animal data is basically a range of how much more susceptible the most susceptible person is and we think that's roughly three to five logs over what a standard normal person would be.

And our other main piece of data is we think there are 20 percent of the population that for one reason or another are more susceptible than a normal person. And so the big trick after that is to develop some distribution which assigns how many people are how many logs more susceptible, and I may do this as one distribution, but actually now my current thinking as of today is that I will break this up into different categories. I'll probably have a separate category for gastric acid secretion. I think maybe gastric acid secretion that looks like instead of three to five logs more sensitive is two logs more sensitive, and I think we also have some data on exactly how many people fall into that category. So I think actually I can do a pretty good with gastric acid secretion.

And that would still leave the other categories of people who are more susceptible which includes pregnant women and immuno-compromised persons. I will also develop distributions for those. Probably the immuno-compromised category will cover that three to five dose--log dose range,

but the question is--I think the big question how immuno-compromised are they and are they any closer to five logs or zero logs?

And I'll probably--I mean I guess my current thinking right now is I'll have some, roughly two, I'd say I'll use a triangular distribution with those bounds, zero logs and three to five logs as an uncertainty bound, and then a one to two most common, an adjustment of one to two logs as the most common immuno-compromised person. And if you can think of a better way of doing it, I'd like to hear it.

Okay. And here's what basically I just said. I did write it out except instead of--except I was originally thinking 20 percent of the population. I think now I can break it out to gastric acid secretion as a separate category so this would just apply to the remainder.

All right. Then rodent to man, I think the main reason for having this adjustment factor is I think there is a little bit of evidence suggesting that humans are somewhat less sensitive than say mice or rats, which mainly comes from--there's one study that had one monkey in it, and they repeatedly challenged this one monkey and at least as far as this one monkey goes, it took roughly ten to the ninth

Listeria to make this particular monkey sick, and challenges of ten to the sixth and ten to the fourth didn't.

And then also if you look, there is one epidemiology study, which we didn't present, but--no, I guess that was the chocolate milk outbreak where something like, at least if you believe the dose, and that's part of the answer, anyway if you believe the dose, I think there were 50 people exposed to something like ten to the 12th Listeria and the only symptom were gastric symptoms. So there was no, I think there were a few cases of sepsis, but there were no lethalities, a few cases of sepsis, and that's it.

So if you take that study at face value, and there are other ways to explain it. Maybe it was a non-virulent strain, maybe the diarrhea actually protected them from Listeria, and what's in that one--maybe they were particularly insensitive individuals, but nonetheless that study makes you think that maybe people aren't quite as, at least normal people aren't quite as susceptible to Listeria as mice.

All right. Now I'll get to the dose-response itself. This is--I mean the reason you have this shift at the dose-response modeling function where you go from talking about a meal to having the group and the dose group

is because these models are population models. You're not really modeling what happens in an individual. You're modeling the frequency at which something happens in a population.

And there's two different endpoints I've undertaken to model so far. One is lethality in mice which is the LD-50 data and then there's also another data set which has somewhat more animals in it which is modeling infection which I think can at least loosely be taken as a sepsis model.

And I use this data by fitting five different models and also using statistical technique to represent sampling error from the study. That's particularly important in the mouse study because there is not very many animals. And here's the mouse data and actually there is another study. There's another study I'm going to add to this. But here's an example of a model fit to that mouse data I just showed. That's the blue data. The blue data points are the normal mice. There's also--I have plotted on there some susceptible mice which sort of shows you the susceptibility range for those mice. I mean the problem is in interpreting the defect these mice have relative to humans. It's not clear exactly how that correlates.

And then here's the larger rat study. It has more animals, less sampling error, and I don't have this--I have some more models, but they're on a different computer and I might show that to you later. I'm not sure it's important, but I guess the main thing I'd point out about this, the rat--this rat study versus the mouse study is that the lethality data in mice makes it look like you got a very narrow range that goes something from like, it goes from zero percent lethality to 100 percent lethality over a two-dose log range, which may be due to the fact that the mice are more inbred or they had more control of conditions.

But in any case, this rodent study you're covering seven logs and you go from--you still have some incidents at this low dose and you still haven't gotten to 100 percent lethality up at ten to the ninth. So at least taken at face value, this makes it look like there's more variability in infection and lethality, but it also may be attributable to the small sample size for the mice or some other, or this less control with the rats. And that's all I got, I believe. Yes. Now we can talk about it.

COMMITTEE DISCUSSION

CHAIRPERSON WACHSMUTH: Okay. Any questions for Clark? Okay. It's just about ten after two. Why don't we go ahead and open it for general questions now. Questions

for any of the panel presenters? Perhaps concluding remarks if there are no questions? Or no? Okay, Michael.

DR. GROVES: I have one question for your dose-response, did you challenge these animals with a mixture of different strains or one of the strains? Maybe you mentioned and I may have just missed it.

DR. RAYBOURNE: Single strain, one strain.

DR. GROVES: A follow-up. Is there any, to your knowledge, any information that if you challenge them with the effectiveness of lack of effectiveness of challenging with several strains versus just one? I mean in foods, as you showed in some of your data, there may be multiple strains in foods so I'm just wondering if you are planning on looking at in addition to one strain mixing strains?

DR. RAYBOURNE: I guess the answer to that would be if studies are out there that are using multiple strains, we didn't consider them in this, in this presentation, and, you know, of course, it would be interesting and worth looking at to include, to consider them and look at those as well, but we didn't do that. I don't know if that answers your question or not, but--

CHAIRPERSON WACHSMUTH: Nancy.

DR. NAGLE: I have a question. I think I'd like to go back to Patrick, our first speaker. You mentioned in

your review of the data from Italy that all four of those foods you found Listeria in them, but--or in three of the foods Listeria was found, but really it was the rice salad that was implicated epidemiologically?

DR. McCARTHY: That's correct.

DR. NAGLE: Does that raise a concern for using some of that one instance data that's on your last page there where there's only one person that's ill and we have a food that we've kind of implicated, but how well have we implicated it?

DR. McCARTHY: Well, could you help me by identifying that particular study that you're referring to?

DR. NAGLE: Let's see. It was on your second-to-last slide. Well, let's see, the first, the Italian data was in your fifth slide.

DR. McCARTHY: Right. I have the Italian data.

DR. NAGLE: Right and then your second to last slide, you list all of those outbreaks and then you attribute a food to them in a strain and I'm just looking--where you said there's either one or two people that have been sick.

DR. McCARTHY: Right. I'm looking at that.

DR. NAGLE: Okay. I guess my concern is should we take any of those foods as really the source when if I look

at this Italian one, it looks pretty obvious that maybe it was the shrimp or the cream cheese or the fruit tart, and yet you come back and say that it was none of those, it was the--

DR. McCARTHY: Right. I think--

DR. NAGLE: --it was the rice that was--the rice salad that was implicated.

DR. McCARTHY: I think that you've identified another problem with the epidemiology in terms of identifying foods and reporting completely. I can only--what I reported here was what I was able to develop in the literature, but I think that you're right when you say that there's a possibility that more foods could be involved that have been reflected in the report. So I thought that that Italian study was kind of interesting too in that when all was said and done, they implicated the rice salad although they never actually conclusively showed that the rice salad had the serotype in question. So I agree with you. I agree with your insight that it's very difficult to rely on these studies.

CHAIRPERSON WACHSMUTH: John.

DR. KOBAYASHI: Let's see. I have a question with regards to that chocolate milk outbreak. Did you speak with the investigators as to how that information was obtained on

the amount consumed? Because I agree with you, I mean at 10 to the ninth bacteria per cc, it would seem that that would resemble more buttermilk than chocolate milk, and one wonders how you can consume 240 ccs without noticing that?

DR. McCARTHY: I have not talked with the authors there, although I do have plans to talk with the authors of different studies. I'm talking with the author of the Finland study and also I will be talking with and I have talked with the author of the Los Angeles outbreak study, but the particular study that you have identified, I have not had a chance to talk with the author yet.

CHAIRPERSON WACHSMUTH: Dr. Buchanan.

DR. BUCHANAN: Just a follow-up comment on that. I have personally done inoculated milk studies and have held milk for up to a month with Listeria inoculated into it at the end of that month, even though the levels of Listeria had been and stayed between ten to the eighth and ten to the ninth per ml, for that total length of period, the milk other than a slight off-flavor or off-aroma--we didn't taste it--

CHAIRPERSON WACHSMUTH: Very good.

DR. BUCHANAN: Other than a slight off-aroma, which would have certainly been masked by chocolate, there

was no apparent difference in it and fresh milk. So it had no real organoleptic impact on the milk.

CHAIRPERSON WACHSMUTH: Swami.

DR. SWAMINATHAN: Yeah. I just want to add to that and I vividly remember one of the cases from that describing the organoleptic properties of that milk, and he identified himself as a connoisseur of milk, and the only thing that he said was he took a sip of that milk, and he said this was not good milk, it had a woody flavor and a cartony flavor and then he kept on sipping and sipping to see what was wrong with that milk, and that's how he probably finished the 240 mls.

CHAIRPERSON WACHSMUTH: Nancy.

DR. NAGLE: I'm sorry.

DR. KOBAYASHI: I just have a comment that maybe is obvious to those collecting the data, but in general up until quite recently with the DNA fingerprinting of listeriosis, it's been very, very difficult, at least as far as I'm concerned, to identify sources of outbreaks with regards to listeriosis especially with small clusters of cases. The incubation period is rather long and I can't tell you how many times we've seen relatively small clusters of cases, thought something was going on, but went nowhere in terms of the investigation.

And I guess my advice is to keep that in mind with regards to some of the quantitative data on amounts of Listeria in the implicated products. It may well be that those will be lower once better epidemiologic tools are available to identify sources of infection. It's kind of interesting that the most recent outbreak with hot dogs, the colonies cfus are rather low in comparison to the earlier outbreaks. I don't know the story about Finland, but it also was a relatively recent outbreak.

DR. CARRINGTON: Well, I guess--

CHAIRPERSON WACHSMUTH: Go ahead, Clark.

DR. CARRINGTON: I think, I mean at least one of the problems with the some of the outbreak dose measurements is they're not the food as consumed. They're at some point earlier. And I think we could still, you know, possibly make use of it by putting the numbers into the rest of the model. In other words, we'll put the numbers in and then we'll model growth and see if we get the number and then run it through the dose response model and see if we get the number of cases we expect.

If we don't, it makes it a lot harder to tell what part of the model is wrong because there could be something wrong with the dose-response or the growth model or anything

else in between. But nonetheless, it can still serve as a check of some sort.

DR. LONG: I think we're asking here about the usability of these different epidemiological studies. Folks, this is what we've got. And I guess from what I'm hearing I think is that there might be some validity in the chocolate milk numbers, but that we should think seriously about using the Italian study where rice salad appears to be the vehicle but it was never isolated from rice salad. Does anyone have comments on any of those other--I guess there were just three other studies that Pat mentioned. And also the issue of using a study where there's a single case but there's a dose.

CHAIRPERSON WACHSMUTH: Okay. Roberta had her flag up, but do we want to finish--is it related to this?

DR. MORALES: It's a different question.

CHAIRPERSON WACHSMUTH: It's a different question. To this point, Bob?

DR. BUCHANAN: First, I'd like to apologize to Pat for not being here for your presentation. I did want to give some comments on--I heard the investigators from Finland make a presentation on this outbreak last week. Two points that they brought out in the discussion in their presentation was that while most of the samples they looked

at were low, less than 100, there was one that over 11,000 per gram, and the second item is that the investigator one questioned during the question and answer period indicated that Listeria would grow in the butter.

CHAIRPERSON WACHSMUTH: Swami.

DR. SWAMINATHAN: About the rice salad, I want to correct a statement. It is not that Listeria was not isolated from the rice salad, but rice salad was not available for testing. I think there's a big difference between the two.

The second thing is in our sporadic listeriosis study when we would obtain the refrigerator contents of listeriosis patients and then analyze several foods that were in the refrigerator and freezer, in many instances we found the same strain of Listeria monocytogenes in multiple foods from the patient's refrigerator indicating that at some point the cross-contamination had occurred, and I think that's the same kind of scenario that we could easily envision for the Italian outbreak as well.

DR. LONG: Dr. Swaminathan, are there some published reports of that? Pat is aware of them. Okay. Yes.

CHAIRPERSON WACHSMUTH: Okay. Michael, is your point to this?

DR. DOYLE: It's relative to Wes' original question. This is Mike Doyle. And I have, I guess, some concerns about how the data from the chocolate milk outbreak might be extrapolated. It seems to me like most of the individuals that were involved, if not all the individuals involved, were normal healthy humans. I didn't know of any pregnant women that had drunk that milk, and so we didn't see anything more than gastrointestinal response, and secondly we're raising questions about variability among the serotypes or strains of Listeria monocytogenes and I can't recall. I think this was a 1/2 a or b versus a 4b, and there's a lot of factors that come into play here. And to say that it's going to take ten billion or whatever cells to produce illness, well, it certainly would be for that strain and that host population. But how are we going to extrapolate those data to pregnant women and immuno-compromised?

DR. LONG: Well, I mean that's the challenge if doing a quantitative risk assessment on Listeria that tries to relate dose to susceptible subpopulations. If we want to do a quantitative risk assessment, this is really the information we have. So we're going to have to make assumptions.

And we're going to spell those assumptions out as clearly as we can. Hopefully, the uncertainty in those assumptions will be reflected in the model and in the range that the model ends up showing, but I can turn that question back on you. Is the take-away from that saying the chocolate milk study is such an outlier from the epidemiological record that perhaps we should throw it out completely from the analysis or are you saying something else?

DR. DOYLE: Well, what I'm saying is that the major problem that we've had with listeriosis is its effect on pregnant women and immuno-compromised populations, and it's an outlier in the sense that it's affecting the healthy population, but the serious illnesses, which I'm most concerned about, would not be encompassed by these data.

DR. LONG: So the only thing--I think what you're saying is then that the chocolate milk data really would only be useful for the normal individual, but it doesn't address the immuno-compromised?

DR. DOYLE: That's the way I'd interpret the data, yes.

CHAIRPERSON WACHSMUTH: Okay. Roberta.

DR. MORALES: Well, this was originally an unrelated question, but it may be a little more related now.

I actually think this is a very neat approach and I'd like to commend the group for coming up with this innovative approach to looking at dose-response when you don't have a whole lot of human data.

My question is somewhere some of those studies you showed had mice studies which had a bunch of different--you had controls for all of those different studies. I'm wondering if maybe one of the approaches to sort of get at but not quite to the point that you're bringing up, Mike, is to maybe separate that data so you use your control studies as representatives of your say normal population and then use the studies where you've got the knock out mice for some kind of representation of your immune compromised population.

DR. LONG: Thank you, Roberta. I think that's exactly what we're going to be doing. The animals show the range of susceptibility. We have very little human data on which to anchor that range of susceptibility, but because we don't have the data in pregnant women, the quantitative data or in the elderly, then we're going to have to bridge between the animal data and the available human data to try to characterize those populations.

DR. POTTER: Wes, can I ask a follow-on question to that just as a point of clarification? Are you

suggesting then that the animal data tell you the shape of the curve and then the epidemiologic data from outbreaks tells you what the scale is?

DR. CARRINGTON: That's basically the idea, yeah. That's essentially the way it works. But let me just--as far as the chocolate milk data goes, I think there's, at least the way the model is set up now is that how--there's a species difference issue and then on top of that, there's a host susceptibility issue.

And the species adjustment factor is intended to adjust, you know, from normal mice to normal humans. That's the idea and that's why I brought up the chocolate milk in that context. I think that's some evidence that normal humans are less sensitive than normal mice.

On top of that, there is going to be another adjustment which pushes dose back the other way for pregnant women. And also I think we regard it as actual two issues. One is that they're more susceptible and they're more likely to get sepsis from a given dose, but I think the other issue with pregnant women which comes on top of that is the consequences of getting sepsis are worse. In other words, you get infected, instead of a temporary illness, you get a stillbirth and both of those things are happening and those

both contribute to the overall severity of the illness in pregnant women.

CHAIRPERSON WACHSMUTH: Alison.

DR. O'BRIEN: Yes. I'd like to just caution you about your conclusions regarding the monkey. You certainly made the caveat you're dealing with one monkey, but your interpretation is that humans might be, normal humans might be resistant than normal mice using the monkey as a surrogate for human. The caution comes from what we know about another microorganism, Shigella, which is, we know from oral, studies with people, that the oral infectious dose might be as few as ten organisms, but in the monkey it's somewhere around ten to the ninth or ten to the tenth. And the mice aren't susceptible at all.

That's one caveat and the second is that you pointed out that most of your mouse studies were not oral. Is that correct?

DR. RAYBOURNE: That's correct. There was one I think that Clark used in his susceptibility model--

DR. O'BRIEN: I don't mean your studies. You didn't design the studies. Most of the studies you found were not oral.

DR. RAYBOURNE: Yes.

DR. O'BRIEN: And that does also affect I think the relationship of dose-response no matter what the species. Certainly in mice, if you took Salmonella typhimurium and you infected them orally, you might have-- for Balb C mice, you might have an oral LD-50 of ten to the fifth, but if you injected, it might be less, ten or less. So it does affect your interpretation.

DR. LONG: To repeat what's being said up here, the neutrophil study was oral, but the others were IP studies. So I guess the question to turn back to you, Dr. O'Brien, is these were the only studies we were able really to find that met enough of the data needs and criteria to be considered useful. Do you think then that the studies, the limited number of studies that we've described for the animals, the way we intend to use them is valid?

DR. O'BRIEN: Well, I have a lot of concerns about directly correlating dose between that type of animal model and humans because overall dose, what we do know of correlation as in Shigella and even with the monkey as I said, there really isn't a strong correlation with the actual numbers and since this whole issue is about quantitation, I would be wary.

DR. LONG: And just to reinforce one of Dr. Raybourne's early slides was that, and just to remind

everyone here, we're not thinking that the animals are a direct correlation to the humans. But we do see is that range in the animals and it's, in fact, that range of susceptibility or that range of strain variability that we do intend to apply directly to the limited human anchor data that we have.

DR. O'BRIEN: Range was a couple of logs, as I remember, which is seemingly more limited than what you're getting in your range of doses that, Rich, you showed in your first presentation for humans. Well, I guess it depends on what you whether you want to call the chocolate milk outbreak relevant or not.

CHAIRPERSON WACHSMUTH: Okay. John Kvenberg.

DR. KVENBERG: Thank you. Sounds like that one poor monkey has been through a lot. Notwithstanding the caveats on primates, the data you have so far largely is rodent associated. I thought there were plans afoot in studying a primate model, principally a chimpanzee, which is close. Is that an area of data gap or what--I guess I direct this to Rich Raybourne--as far as a suitable animal model, species of primate--

DR. POTTER: It's Rhesus, not chimp.

DR. KVENBERG: --that would be utile in working on an animal model. Is there anything known about that?

DR. RAYBOURNE: There's an ongoing study using Rhesus mecax, a Rhesus mecax I think is what they're called, Rhesus monkeys. And so we're anticipating getting some data from that study as well. Don't have it yet though.

DR. LONG: Even with the primates, there are ethical issues and we were very lucky in this situation to have a natural infection of Listeria in this monkey colony so this study was a very nice bit with a very serious problem that they have in the colony.

CHAIRPERSON WACHSMUTH: Spencer had his flag up and then Swami.

DR. GARRETT: Yes. Thank you. Spencer Garrett with the National Marine Fisheries service, and I surely do feel like a fish out of water asking this question. But just kind of listening to this, obviously there haven't been any studies, but are any complicated or any contemplated using pigs, which has a little bit more trans-genera similarity? I would think you could get the elderly. You could get the pregnancy questions addressed. I'm not quite sure in terms of the approval for the study, but it would just seem to me that, of course, you can always have a better risk assessment with new data. We all know that, but I was just kind of wondering if--I mean why a fish guy would think of that--could you shed any light on that?

DR. RAYBOURNE: Unfortunately, no. I didn't come across any pig experimental studies and I don't know of any that are planned.

CHAIRPERSON WACHSMUTH: What was the problem in the monkey colony? Spontaneous abortions?

DR. RAYBOURNE: Yeah.

CHAIRPERSON WACHSMUTH: Okay.

DR. POTTER: I don't think the veterinary literature has very much about spontaneous listeriosis in swine. Most of the veterinary literature on listeriosis is restricted to ruminant animals or horses, the horses almost exclusively on encephalitis. So it may be that there are striking susceptibility differences in swine. It could also be that they have it and I don't know about it.

CHAIRPERSON WACHSMUTH: Swami.

DR. SWAMINATHAN: As far as animal studies are concerned and oral inoculation, the late Dr. Leo Pine at CDC has published at least two papers on that subject, and if you don't have those papers, I'll be happy to supply them to you. And the second thing, as far as human exposure is concerned, I can tell you about one incident that you may not be aware of because this is not in the literature, Felix Leisner in Kulmbach, Germany called me--this was several years ago--very excited because his technician was mount

pipetting Listeria monocytogenes--I remember it was a serotype 1/2a--and swallowed some Listeria and he had carefully quantified how much Listeria she had swallowed. Unfortunately, I got a follow-up call from him saying that she suffered no symptoms whatsoever. But that's one that you may want to be aware of.

DR. LONG: And that raise a very good point that a lot of the data we're missing is the people that ate it and did not get sick and that's one of our biggest problems with the epidemiological record.

CHAIRPERSON WACHSMUTH: Okay. Bob.

DR. BUCHANAN: Yeah. It appears that your best oral dose data in humans is for normal humans through the chocolate milk study and the primary endpoint there was diarrhea. It appears that your best data available on the differential between immuno-competent and immuno-impaired is the animal model data that you can get pretty much, say, a difference in the dose that produces a certain response.

If you take the human feeding data from the chocolate milk outbreak and extrapolate, move that curve to the left, the appropriate number of logs based on the animal data, the difference between immuno-impaired and immuno-competent, what kind of dose response would that give you for the impaired humans?

DR. LONG: Are you asking us for a number, Dr. Buchanan?

DR. BUCHANAN: I'm asking you have you looked at that?

DR. LONG: That is certainly our approach.

DR. BUCHANAN: Okay.

DR. CARRINGTON: All right. Well, I think there is two problems. First of all, the most you get out of the chocolate milk study is a data point. You don't get a curve, you just get, you know, but you do get a attack rate at one dose, which is--actually that's the most you ever get out of any epidemic is one data point, but if you put enough of them together, then you get a curve.

But the other problem is they had the wrong endpoint. That's not the endpoint we're looking for, and so--and it doesn't even compare to any of the animal models and we're not even--the other thing about that study is there were a lot of other bugs they were exposed to, and it's not--I'm not all that sure--I guess there was some doubt as to whether or not the diarrhea was actually the result of Listeria.

So I guess that makes it pretty hard--so I mean I guess my main interpretation of that study is almost as a negative data point and that so many people got exposed with

that dose and none of them died. So I mean it doesn't tell you what the attack rate is for lethality except that it's less than one over 40, you know, one over 60. So I mean for normal individuals. So that's the main way I think of that study is as one negative data point.

CHAIRPERSON WACHSMUTH: Roberta.

DR. MORALES: In evaluating relative susceptibility, I mean obviously one of the problems with the data that you were able to find is that not much of it is orally dosed. In representing, in talking about your dose-response parameters, you're talking about food matrix, pathogen virulence and host susceptibility, which I think is the right way to go, how are you--and I may have missed this from the presentation, but how are you proposing to reconcile the effects of the food matrix with the host susceptibility data given that not much of it represents oral dosing and that that information is appropriately reflected in the outcome?

DR. RAYBOURNE: I guess ideally we would find a study where there's food involving the effects of food matrix and compromised animals and, in fact, we may have such a data set that we've come by recently that we haven't had within the last couple of weeks or we haven't had a chance to incorporate into this presentation as of yet. So

I think that that--when we do incorporate that, that will help deal with that matrix susceptibility problem.

CHAIRPERSON WACHSMUTH: Alison.

DR. O'BRIEN: Back to the dose issue in humans. In the studies that you didn't discuss because there were no dose data but they were outbreaks in humans, can you garner anything from--I don't know the answer to this--from the mean time to onset to disease? I mean generally speaking, larger doses have shorter incubation periods. I understand that this is a disease that lethal forms or septicemia form is a disease where there is variability in that, but are there differences?

DR. McCARTHY: Well, when I did look at the incubation times, and I asked myself about the same question, the way I categorized it was that the very severe forms, the incubation times were in the days, you know, a week so to months. But in the GI form, in the mild symptoms, they were within hours to days. So if it was a continuum from hours to months, you would have the more severe cases--

DR. O'BRIEN: And that was true for all--basically for all your outbreak data that you didn't have dose on?

DR. McCARTHY: It was just a general statement.

DR. O'BRIEN: Or it was so variable, you couldn't tell?

DR. McCARTHY: It's a general statement and I did not have dose to correlate that observation with.

CHAIRPERSON WACHSMUTH: David.

DR. ACHESON: One of my concerns here is that we really don't know what the virulence characteristics are of LM. And in essence from the presentation what you were saying was that the virulence attributes that we know about, many of them have those and it doesn't really correlate with dose or incubation period of anything else. So there is clearly something else going on with these folks. And it may be that every single one of these studies is using an organism that is different.

And I'm just a little bit concerned about trying to pool all of that and draw too many conclusions when fundamentally we don't know how Listeria monocytogenes makes people sick.

DR. LONG: Can you then propose, can you help us out? I mean we agree.

DR. ACHESON: I should have kept quiet. I mean I think what you're doing is a spectacular job trying to make the best of what we have and obviously we can't do the human studies that we need to do. I mean that can't happen. And

so I think what I would caution you is just overinterpreting what comes out of this and not spending too much time trying to figure out what to drop out, what to keep in, because I don't think there is a really good argument to drop out or keep in much of it.

Just use most of what you've got, but bear in mind interpretation should be limited and use that as you were saying this morning to identify the gaps that the basic science needs to address.

CHAIRPERSON WACHSMUTH: Okay. I'd like to take a break. We'll hear from John first. Then if it's okay with Dick, we'll have the summary after the break, the conclusions, and then have the public comments. John.

DR. KVENBERG: Thank you. This is not a question, it's just a comment to pass on on a personal communication for your consideration. I was in personal discussion awhile back with Jocelyne Recor [?] and she's at the Pasteur Institute in France and has been awarded some amount of monies for mapping the genome of Listeria monocytogenes, if you had not been aware of it. And I guess I don't want to prolong the break, but that goes to the question of the genetics of the organism, just for your information.

CHAIRPERSON WACHSMUTH: Okay. Well, let's take 15 and then we'll wind it up. Thank you.

[Whereupon, a short break was taken.]

CHAIRPERSON WACHSMUTH: Okay. Let's start again. Okay. What I'd like to do to start off the discussion is to have Richard Whiting present the conclusions of the Risk Assessment Team. Then we will open it up for the committee to discuss any of the presentations from today. I think all of the presenters are still here so we could have questions for them individually or to Dick or to Wes. Okay. Dick.

CONCLUDING COMMENTS

DR. WHITING: Okay. Thank you, Kaye. I'm not sure I would describe this as conclusions especially after today. I think with a problem like this that we're addressing, it's quite evident that if the answers were out there and apparent, there wouldn't be any need to do this risk assessment. But I do want to thank the committee for their attention today and for reviewing this, to listen to us. It was very valuable to the team just to go through the process of pulling it together in our minds and making this presentation to you.

And I think we've also gotten some very good suggestions back from you that we will be definitely incorporating into it. I do sense here today, I think, a fairly broad agreement from the committee to the approach and the way we are conducting this risk assessment. If

there is anyone or if there is disagreement with that, please let's bring that up in the next few minutes.

A couple of areas that we definitely will be looking at, which perhaps didn't come out quite as strongly there, we do have dietary information on the normal, pregnant and elderly people, and we will, of course, be trying to look at whether there are differences in the diet amongst this group and whether that will affect potential consumption of Listeria.

And also in terms of the ready-to-eat foods, the idea of putting in that growth period and cooking is to try to get an idea of what the shelf-life factor might potentially be for a food. We can turn that storage module on and off, so to speak, and look at the results with or without it and from that hope to get some guidance into what the effects might be of shelf-life and storage.

As far as a time line for this risk assessment, we are targeting to try to finish this during December and present to the risk managers in FDA and FSIS. I guess I would like to kind of conclude here by saying the risk assessment is a dynamic process and this is the first iteration of it, if you will. This is sort of the broad-brush big picture, look at all of these issues that we've raised, and I think we will probably be looking at some

specific products, specific scenarios, potential mitigations and so on at a later time.

And I would like just to, as a final finish, to say the purpose of the risk assessment here is to try to provide the best estimate that we can around this question. In other words, the best summary of the scientific evidence that is currently available. And in the process of doing that, also make very clear what the evidence supports and what the evidence does not support. In other words, present how good the data is. And I think this is a particularly key point when you think about the dose-response discussion that we've had this afternoon.

This is a very difficult area, as I think all of you appreciate, and, you know, as we try to put this model together, you know, we will try to present the best summary of the information that we can, but we will also be very recognizable and recognize that we have to present exactly what the weaknesses and gaps and so on of this all is as well. So with that, Kaye, I'll thank you and thank the committee.

CHAIRPERSON WACHSMUTH: Okay. Now that everyone has a break to think about all the things you've heard today, does the committee have any other words of wisdom,

questions? Anything else for our risk assessment team? Roberta.

DR. MORALES: Just a comment. During today's presentation, several times the group used terms that--for example, rectangular distribution, which eventually was explained as a uniform distribution, or density, which eventually we figured was enumeration. Just as a request, if you could use, you know, the more common language because everybody recognizes "uniform." It may take some explanation to get to the "rectangular." Everyone recognizes "enumeration." There was a lot of confusion about "density." I think that would help, just up-front, in terms of communicating and getting the baseline information to us as far as what's going on in the risk assessment.

CHAIRPERSON WACHSMUTH: Thanks. David.

DR. ACHESON: I'm not sure whether it's beyond the mandate of the risk assessment team, but are they actually going to uncover the gaps that will come out? Because they're going to be in the best position to realize where the holes are in all of this. Are they going to identify those gaps and recommend specific areas of research or further information that's going to be needed?

DR. WHITING: Well, a typical part of the write-up that the risk assessment would do and has been done in those

in the past is to put a section in at the end of identifying data gaps and perhaps listing research needs that they saw. So, yes, I would expect that there would be a section like you're referring to.

Of course, now this would be just a recommendation from the risk assessment team and nothing more, but, yeah, I think we will do that. I think it is quite apparent, as you saw from today, how despite all of this data that we have on Listeria, how relatively small amounts of it really address the needs of the risk assessment and I think it will be showing perhaps how the broader microbiological community maybe needs to redesign their research and experimentation and reporting of data to begin to make data more useful to risk assessment type analyses. So, yeah, we will have that.

CHAIRPERSON WACHSMUTH: Yeah. I've been struck in this and in the Salmonella egg risk assessment, it's such an excellent way to identify exactly the kind of research that's going to have an impact on the risk, which is I think where we all want to go. So I'm happy that that's going to be an outcome. Bob.

DR. BUCHANAN: And I guess I'm going to ask this question and hope that it doesn't sound too self-serving. I notice in your derivation of where you're going with the dose-response models that you--I didn't see any slides on

the ones that have already been published that have been derived from alternative means. These have been looked at at least twice by two different groups. One by the Canadians most recently and then also there's a risk assessment group over in Europe that have been doing work on Listeria.

And they've evaluated the various published dose-response models that have been derived from a whole different approach, and they seem to find that they're not bad. Do you have any intention of looking at any of those?

DR. WHITING: Well, I'll take the first. Yeah, we're, of course, aware of those, being co-author on one of them. Those studies, what they did for people who aren't familiar with it, is came from Europe where there is quite a bit of consumption of products like smoked fish where they have some enumerative data and consumption data on those products and then that was linked up with the rates of listeriosis. And made some assumptions that most of the cases came from these one or two classes of products so that kind of shrunk the whole risk assessment down to a quite small size and then we could compare the consumption of Listeria within this country with the rates of listeriosis within that country. And, yes, it does give a certain measure.

But the problem, of course, you don't have any direct comparing of the person of consumed Listeria with that particular person's consumption, you know, so it's sort of like putting two separate independent, you know, bits of data together. So that's, I think, the reason our group tried to work through this other approach that we showed you today, but, you know, we are aware of those and we certainly will mention that they are there and put them up for the people to evaluate.

CHAIRPERSON WACHSMUTH: Morrie.

DR. POTTER: I think that's a very nice response, Richard, and, in fact, I think the approach that your group is taking addresses some of the concerns that reviewers of the other paper down at CDC had with some of the assumptions that are necessary to link those two covariables, and so I think that the structure that follows sort of the Codex model and the more classical model of risk assessment from the red book and the approach taken in some of the standardization of default assumptions or for the assumptions may help its more general acceptability.

So I think that that's not to say that the other approaches are not valid, but I think that the approach does address some of the or does address some of the concerns about the other approach.

CHAIRPERSON WACHSMUTH: Okay. I think that concludes Listeria monocytogenes risk assessment discussion. I think it was very nice. Thank you. The team has done a great job.

And now it's time for public comments and we do have one registered presenter. Caroline, are you with us? Microphone.

PUBLIC COMMENT

MS. SMITH: Where's Bernie? Doesn't the industry always talk during these? I'm not used to going first. I'm Caroline Smith, Director of Food Safety with the Center for Science and the Public Interest, and I'm talking today briefly on the Listeria risk assessment. We've had an observer here all day, Darren Mitchell, who couldn't stay till now, but he filled me in on everything he learned during the first session.

And basically what we're taking--the take-home message for us is that we are years away from having real answers on dose-response and many of the questions facing us on Listeria monocytogenes. There are huge data gaps which this risk assessment team is dealing with and doing a very good job. It's a good effort, but it's a long way, many years, before we're going to have solid answers.

I think there is no evidence at this point to support any change in the zero tolerance in ready-to-eat foods and in addition, it's clear that we cannot wait for the completion to fill all these data gaps for the completion of this work for USDA to take regulatory action on Listeria monocytogenes.

CSPI will petition FSIS to develop a regulatory response for enforcing the zero tolerance for Listeria monocytogenes in ready-to-eat meat and poultry products this fall because we just are not confident that the agency's steps so far are going to prevent the kind of outbreak that we saw with the Sara Lee products. 20 people dead and 100 illnesses should be enough to support rulemaking. And we just can't wait to have all of the answers before the agency takes action. Thank you.

CHAIRPERSON WACHSMUTH: Thank you, Caroline. Any other comments from anyone else who didn't register? Anyone outside of the committee? Okay. Any comments from anyone at the head table? We're out of here. Have a good evening.

[Whereupon, at 3:30 p.m., the committee adjourned, to reconvene at 8:00 a.m., Friday, September 24, 1999.]

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