
**U. S. Food and Drug Administration
Center for Food Safety and Applied Nutrition
National Advisory Committee on Microbiological Criteria for Foods
December 8-10, 1999**

National Advisory Committee on Microbiological Criteria for Foods

Meeting on Fresh Citrus Juice

Transcript of Proceedings

Volume I: Wednesday, December 8, 1999

Volume II: Thursday, December 9, 1999

Volume III: Friday, December 10, 1999

Volume III Friday, December 10, 1999

PARTICIPANTS

COMMITTEE MEMBERS

James D. Anders
Dane T. Bernard
James S. Dickson
Stephanie Doores, Pennsylvania State University
Michael P. Doyle
Mel W. Eklund
Daniel L. Engeljohn, Ph.D.
Michael G. Groves
Michael L. Jahncke
John M. Kobayashi
John E. Kvenberg
Earl G. Long
Roberta A. Morales DVM, Ph.D.
Marguerite A. Neill
Michael C. Robach
Leon H. Russell, Jr.
Skip Seward II
William H. Sperber
Bala Swaminathan, Ph.D.
Robert B. Tompkin

AGENCY REPRESENTATIVES

Janice Oliver, Deputy Director, Center for Food Safety and Applied Nutrition, FDA
Arthur P. Liang, MD, MPH, CDC Liaison
LeeAnne Jackson, FDA Liaison
Dr. Karen Hulebak, Executive Secretary

ALSO PRESENT

Dr. Paul Mead
Dr. Dale Hancock
Dr. Colin Gill
Dr. Isabel Walls
Dr. Charles Haas
Dr. Nancy Stockbine
Dr. Bonnie Rose
Dr. Mark Powell
Dr. Eric Ebel
Dr. Wayne Schlosser
Dr. Tanya Roberts
Ms. Peg Coleman

CONTENTS

AGENDA ITEM

- Introduction of Risk Assessment Team - Karen Hulebak, Ph.D.
- Introduction and Scope - Mark Powell, Ph.D.
- Overview of Model Segment Outputs (Best Estimates) and Exposure Assessment Validation - Eric Ebel, D.V.M., M.S.,
- Wayne Schlosser, D.V.M., M.P.H.
- Production - Eric Ebel, D.V.M., M.S.
- Slaughter - Tanya Roberts, Ph.D.
- Committee Discussion
- Lunch
- Preparation - Wayne Schlosser, D.V.M., M.P.H.
- Dose-Response - Ms. Peg Coleman
- Model Summary, Epidemiological Validation - Mark Powell, Ph.D.

PROCEEDINGS

MS. OLIVER: Good morning. Once again, my name is Janice Oliver, and I'm Deputy Director for FDA's Center for Food Safety and Applied Nutrition.

I don't have to keep Bob Buchanan in place today. I just have to keep Dane in place.

DR. BERNARD: Yes, ma'am. What is this, "pick on Dane" day? Bruce is over here giving me all kinds of grief.

MS. OLIVER: I've got to pick on somebody, Dane.

I'll be chairing the meeting again today. Dr. Kaye Wachsmuth is not able to be with us. However, Dr. Hulebak is here this morning from FSIS and will be assisting me in chairing the meeting.

This morning FSIS is going to be presenting risk assessment models for E. coli 0157:H7. What they'll be doing is there will be various presentations throughout the day. The presentations are geared at about 45 minutes each, allowing 15 minutes afterwards for questions. The questions, as in the previous day, will be primarily for the Committee and the invited experts to ask questions. If there's still available time, then we'll ask those others who are here at the meeting if there is time to ask questions also.

First, the Committee is supplemented today by a number of experts that FSIS has invited. I would like to turn it over to Karen Hulebak to introduce those, and then after that, I will ask the entire Committee and the experts to introduce themselves again for the record.

DR. HULEBAK: Good morning, everybody. Thank you all for being here to listen to this presentation by our risk assessment team of our risk assessment for E. coli 0157:H7 in ground beef.

In order to assist the Committee and to add to its expertise, especially in view of the fact that David Acheson and Alison O'Brien can't be here today, we've invited a number of experts to take part in this discussion, some of whom have arrived and, I believe, some of whom have not.

Here with us presently are Dr. Isabel Walls, NFPA; Dr. Colin Gill of Agriculture and Agrifood Canada; Dr. Paul Mead of CDC; Dr. Nancy Stockbine of CDC, expected; Dr. Chuck Haas of Drexel University; and Dr. Dale Hancock of Washington State University.

I'd like next to introduce the risk assessment team, the FSIS risk assessment team. They are seated at the back of the room there. Most of these folks are from the Food Safety and Inspection Service. The team is headed by Dr. Mark Powell, and the members of the team include Dr. Eric Ebel, Dr. Wayne Schlosser, Dr. Peg Coleman, and Dr. Tanya Roberts, who's with USDA Economic Research Service.

We have a full day of presentation and discussion for you. We'd like to take this day to make sure that you hear from us in an appropriate level of detail, that is, enough detail to inform you about our assumptions and the model parameters and the outputs of the model with a degree of detail that informs you and doesn't overwhelm you or, worse yet, bore you.

There are several questions that we'd like you to keep in mind as you listen to the presentation. With these questions, we hope to focus your thinking about particular aspects of the model, but please don't assume that this is all we'd like you to--that this is all we seek your comment on. We would like you to consider these particular questions, but we welcome your comment on other aspects of the model or other questions of the model that you might have.

You have them before you. The question about resolution we will leave for later. We may not get to it at all today, but we would like you to consider the second bullet there: Is there evidence that would allow us in this model to adjust for the specificity of microbial analysis? That's our major cross-cutting question.

With respect to the production section of the model, can the Committee recommend a better way to link live cattle to contaminated carcasses, the link that we try to

make in this model?

Are there data or methods currently available that would improve the quantitative links among fecal, hide, and carcass contamination? With respect to slaughter, what evidence would be necessary to satisfactorily quantify the link between hide and carcass contamination?

Second, with respect to slaughter, we've attempted to develop a model, a mechanistic model that follows product through the slaughter plant. Would it be preferable to develop a strictly data-anchored model which does not attempt to model processes between monitoring plants? If that were possible, what data would be required to develop such a model?

Regarding preparation of product, rather than modeling beyond the last point where validation is currently possible for raw ground beef, would it be preferable to consider simply a proportional relationship between the prevalence of 0157:H7 in raw ground beef and the incidence of 0157:H7 illness due to consumption of ground beef?

Next, for preparation, how do we define a plausible frequency distribution for extreme time/temperature handling conditions in the absence of data?

And then, finally, for dose-response, are there sufficient data and methods available to develop a separate dose-response relationship for the susceptible sub-population? How might we validate such a curve?

Is the basic envelope approach sound? And you will hear more about that, of course, during the discussion of dose-response.

Is it appropriate to anchor the most likely value for the dose-response, the beta plus one envelope. The envelope describes the various assumptions made about dose-response covering the range of what we know.

Again, please think about these questions as the ones that we would most like to hear from you on. Do not limit your questions or your commentary to these particular questions.

Also, while this is the one day we have to present this full model to you, we hope you take the opportunity in the coming couple of months to give us whatever suggestions you have and ask us whatever questions you have. There's some work we have yet to do on this model, and we have time to incorporate any thoughts that you might have.

Any questions at this point?

[No response.]

DR. HULEBAK: All right. Then let's dive right in.

MS. OLIVER: Let me just ask the Committee before we go further to introduce yourself for the record since several members are not here that were here earlier, and I'll start to my right, please.

DR. WALLS: Isabel Walls with the National Food Processors Association.

DR. GILL: Colin Gill of Agriculture Canada.

DR. RUSSELL: Leon Russell, Texas A&M University.

DR. JAHNCKE: Mike Jahncke, Virginia Tech.

DR. GROVES: Mike Groves, LSU.

DR. DICKSON: Jim Dickson, Iowa State University.

DR. SPERBER: Bill Sperber, Cargill.

DR. ROSE: Bonnie Rose, FSIS.

DR. SWAMINATHAN: Bala Swaminathan, CDC.

DR. MORALES: Roberta Morales, Research Triangle Institute.

DR. ANDERS: Jim Anders, North Dakota Health Department.

DR. LIANG: Art Liang, CDC.

MS. JACKSON: LeeAnne Jackson, FDA CFSAN.

DR. ENGELJOHN: Dan Engeljohn, USDA FSIS.

DR. DOYLE: Mike Doyle, University of Georgia.

DR. DOORES: Stephanie Doores, Penn State University.

DR. ROBACH: Mike Robach, Conti Group Companies.

DR. KVENBERG: John Kvenberg, Food and Drug Administration.

DR. NEILL: Peggy Neill, Brown University, Providence.

MR. SEWARD: Skip Seward, McDonald's Corporation.

DR. LONG: Earl Long, CDC.

DR. TOMPKIN: Bruce Tompkin, ConAgra.

DR. BERNARD: Dane Bernard, NFPA.

DR. HANCOCK: Dale Hancock, Washington State University.

MS. OLIVER: Okay. Thank you very much.

With that, Mark Powell will now give the introduction and scope of today's meeting.

DR. POWELL: Thank you. Can everyone hear the level fine? Bring it in closer? There, is that good? Okay.

Well, thank you. On behalf of the USDA Food Safety and Inspection Service E. coli 0157:H7 risk assessment team, I'd like to thank the participating agencies, members of the Committee, and the other invited experts for providing us this opportunity to present the draft FSIS risk assessment of E. coli 0157:H7 in ground beef. The agency views your input as a key element of the scientific peer review process that underpins informed food safety decision-making.

Today we will be presenting the draft baseline process risk model, that is, we will be presenting the model of the as-is scenario that reflects the existing range of practices and behaviors regarding the production, slaughter, processing, preparation, and consumption of ground beef in the U.S. The baseline model does not include any assessment of the potential public health impacts of alternative risk mitigation measures, and our purpose in presenting the draft model is for scientific peer review, not for discussion of the risk management options or the policy implications of the draft model.

Next slide?

The full risk assessment team consists of members in addition to today's presenters. The team has also received significant contract support as well as input from IFRAG, the Interagency Food Risk Assessment Group, which is convened by the USDA Office of Risk Assessment and Cost/Benefit Analysis, and we'd like to take this opportunity to recognize their contributions. In the interest of time, the presenters will refer to E. coli 0157:H7 simply as 0157.

Next?

I will lead off today's presentation with some background and a definition of the scope of the assessment. Eric Ebel will then summarize the outputs of the exposure

segments of the model, and Wayne Schlosser will present our efforts to correlate the exposure segments of the model with surveillance data. After a brief break, Eric Ebel will present the production segment, and Tanya Roberts will present the slaughter segment before lunch.

Wayne Schlosser will begin the afternoon session with the preparation segment, followed by Peg Coleman with the dose-response analysis. I will conclude the presentations with a summary and then a comparison of the model's predictions with an epidemiologic estimate of the annual number of cases of 0157 due to ground beef. For most of these segments, we have budgeted 45 minutes for the presentation and 15 minutes for questions and discussion.

Next?

This slide places the assessment into context. Since 1994 FSIS has treated raw ground beef with 0157 as adulterated under the Federal Meat and Inspection Act unless it is further processed in a manner that destroys the pathogen. Most recently, several news sources of information have begun to emerge suggesting that the prevalence of 0157 is higher than previously reported. Recently, FSIS issued a draft white paper on 0157 indicating that the agency is considering its policy in light of this emerging information. The production segment of the draft risk assessment incorporates some of this new information regarding herd and within-herd prevalence estimates. But many of these studies have not yet been finalized or reported in the scientific literature. Future iterations of the model could incorporate new data as it becomes available.

Next?

The 0157 risk assessment project began taking form in March 1998 when I formed a resource group during the formulation stage of the assessment. In October 1998, a public meeting was held to solicit input at an early stage of the process and to release a preliminary document describing the overall modeling approach and summarizing the data that had been acquired by the team to date.

Next?

We have received peer input during the development phase of the assessment through presentations at the Society for Risk Analysis, or SRA, and IAMFES, and by convening a week-long interagency workshop on microbial pathogens in food and water that involved microbial risk assessment practitioners from USDA, FDA, EPA, the UK, and New Zealand.

The peer review process began earlier this week with a presentation of the draft model at the 1999 SRA meeting and continues today with the presentation before this Committee.

Next?

Development of the E. coli 0157:H7 process risk model, or ECOPRM, is intended to address multiple goals, and at this point we have made the most progress towards satisfying the first two goals of developing the baseline model and comparing the predicted results to epidemiologic estimates.

Next?

The scope and nature of the risk assessment is a function of the questions that decision-makers could pose to the analysis. If the only objectives of the assessment were to estimate the magnitude of the problem of 0157 in ground

beef or, alternatively, to establish a risk-based standard for ground beef products at the point of consumption, then it would be sufficient to conduct an analysis of the epidemiologic data or to analyze only the dose-response relationship. The process risk model, however, is intended to provide a broader decision-making tool; therefore, the bulk of the model is the exposure assessment, which contains the analysis of occurrence, growth, and decline of the pathogen from farm to table. Our aim for the baseline model is to be as consistent as possible with the observed data so that we can use the model to identify potential critical control points, evaluate public health impacts of alternative mitigations, and identify key areas for research.

Next?

The 0157 process risk model covers all aspects of ground beef production and consumption from farm to table. In the remainder of my presentation, I'll discuss the scope of the assessment and the range of public health outcomes associated with 0157 in ground beef. The exposure assessment consists of three sequential segments. The production segment outputs the prevalence of 0157 in live cattle. The slaughter segment outputs the prevalence and levels of 0157 in beef trimmings that are destined for grinding. The preparation segment outputs the prevalence and levels of 0157 in consumed ground beef servings. This final output of the exposure assessment feeds directly into the dose-response analysis, and then the final output of the model is the annual number of 0157 cases due to ground beef in the U.S.

Next?

The scope of the assessment is limited to ground beef as a vehicle of infection and, therefore, does not include cross-contamination to or from ground beef or a person-to-person secondary transmission. The scope of the present assessment is also limited to 0157 and, therefore, does not include all enterohemorrhagic *E. coli*. However, the paucity of reported outbreaks due to non-0157 EHECs, combined with the higher isolation rates of serotype 0157:H7 in prospective studies indicates that the other EHECs may not attain the public health importance of 0157 in the U.S.

The scope of the assessment is also annual and national. Although data are available at some points to model seasonal or regional scale, insufficient data are available to model slaughter, processing, preparation, and other processes at seasonal or regional scales.

Next?

The scope of the draft assessment includes cooked ground beef products. The present draft assessment does not include products containing ground beef that are prepared by means other than cooking, for example, fermented sausages. We also have not included raw ground beef consumption, which is a very uncommon practice in the U.S., but the ingested doses would be analogous to very undercooked ground beef, and this is considered.

Intact steaks and roasts are excluded because potential surface contamination would very likely be eliminated during cooking. The present draft assessment does not cover other non-intact cuts of beef such as steaks or roasts that have been blade tenderized or injected with needles that may introduce surface contamination into the

interior muscle tissue. However, FSIS does plan to address the other non-intact products in a subsequent iteration of the risk assessment.

Next?

Infection with 0157 is associated with a variety of public health outcomes ranging from asymptomatic carriage to, in a minority of cases, death.

Next?

The primary risk assessment endpoint is the annual number of cases of 0157 illness due to ground beef in the U.S. This total can be disaggregated into cases of bloody and non-bloody diarrhea; severe cases, defined as cases of bloody diarrhea in which the patient seeks medical care; hospitalizations; cases of hemolytic uremic syndrome or TTP, HUS or TTP; and, finally, the annual number of deaths in the U.S. due to 0157 in ground beef.

Next?

This table characterizes our uncertainty regarding the magnitude of the 0157 problem from all sources and that attributable to ground beef. I'll return later this afternoon to the derivation of these figures from the epidemiologic data, but our best estimate is that about 21 percent of all cases are due to ground beef. Note that there is considerable uncertainty regarding this epidemiologic estimate derived independently from the process risk model. We will correlate this epidemiologic estimate with the results of the baseline model.

Next?

Before concluding, I'll draw your attention to the project's Website. We can provide that to you later so you don't have to copy it down if there's insufficient time. This is where we'll post the risk assessment report and model and other project-related information to make it electronically accessible. In addition, hard copies of the report will be placed in the FSIS docket, and we invite all interested and affected parties to submit comments on the draft risk model and the relevant data to the FSIS docket.

Unless they're brief, I'd ask in the interest of time, since we're running a little late, that we hold any questions or comments regarding the scope of the assessment until the discussion period that immediately precedes our lunch break.

Now I have the pleasure of turning the podium over to Eric Ebel to present the overview of the exposure assessment outputs. Eric?

DR. EBEL: Thanks, Mark.

As we've progressed through this risk assessment process, we've had occasion to present interim reports on the model. Feedback from these presentations has suggested the need for something up front that ties things together and gives the audience a feeling for the big picture of the model. Therefore, we want to begin our discussion of the model with the end in mind.

In this segment, we'll present a general overview of summary outputs from the model as well as how these summary outputs correlate with observed data generated outside the model. I'll be presenting the overview section of this presentation, and Wayne Schlosser will present the correlation section.

Risk assessments are generally broken down into exposure assessments and dose-response assessments. In food

safety risk assessment, the exposure assessment models the occurrence of doses of harmful pathogens in servings of a commodity. For this overview, we'll concentrate on the exposure assessment of the 0157 in ground beef model.

An important--sorry, go back to--I'm sorry. There you go. Okay.

An important principle in resource management is separation of variability from uncertainty. We'll discuss this principle before presenting our results. As we present summary outputs of the model, we will describe the variability in these outputs and the associated uncertainty. We'll consider outputs from the production, slaughter, and preparation segments of the model as all part of the exposure assessment. We won't go into any detail as to how these distributions were derived at this time. Each of the model segments will be discussed in excruciating detail later today.

Variability describes naturally occurring differences that we note within populations or between populations. Variability also results from sampling something less than the whole population.

In the model, frequency distributions represent variability in the system. For a given scenario of the model, we consider these frequency distributions fixed. For example, within-herd prevalence varies from one infected herd to another. A frequency distribution describes the proportion of affected herds at any given time that have, let's say, 1 percent or 10 percent within-herd prevalence. The number of organisms per square centimeter on a contaminated carcass also varies from carcass to carcass. But a frequency distribution describes what proportion of contaminated carcasses have an average of, say, 0.1 CFUs per cm² or 1 CFU per cm².

The temperature that ground beef is exposed to when handled out of compliance with the model food code varies from instance to instance of noncompliance. The frequency distribution of the population of noncompliant handling episodes describes this variability across the population.

DR. POWELL: I just wanted to make the Committee aware that there aren't handouts if you're looking to track this presentation. We have handouts just for the segments that will be production, slaughter, preparation, dose-response. Just for clarification.

MS. OLIVER: Mark, can I ask you to introduce yourself? And I'd just remind everybody that for the recording and for the transcription, if everybody could just reintroduced yourself for the record each time you speak.

DR. POWELL: I apologize. This is Mark Powell of FSIS. And I'll turn the podium back over now to Eric Ebel.

DR. EBEL: In contrast to variability, which is simply a reflection of nature, the concept of uncertainty refers to our confidence in the true value or true frequency distribution of something. Probability in most of our model refers to a measure of confidence. Probability is equivalent to the likelihood of something occurring or being correct. So if we know that variability in the model is represented by a frequency distribution and we are not completely certain of which frequency distribution is the true or correct distribution, we model several different distributions to account for our uncertainty.

Examples of uncertainty in the model include the prevalence of fecal-shedding cattle at slaughter in a given year. There is some fixed prevalence, but we are uncertain of the true fraction. We also know that CFUs per cm² on contaminated carcasses can be described by a frequency distribution, but we are uncertain as to the true frequency distribution. Similarly, the frequency distribution regarding product temperature when out of compliance is uncertain.

As we propagate uncertainty through the different stages of the model, we must consider whether our uncertainty is independent or dependent. Uncertainty describes the likelihood that something is correct. If we are incorrect at the high end of one input, are we more or less likely to be incorrect at the high end of another input? If the answer is no, then the uncertainties in model inputs are independent. Otherwise, they are dependent to some degree.

One technique for modeling independence and uncertainty is called second-order modeling. Basically this involves taking random samples from all uncertainty distributions and evaluating the results conditioned on these random draws. Another technique for handling uncertainty is called boundary analysis. Underlying this approach is the assumption that uncertainty may or may not be correlated. We have chosen this approach for describing uncertainty in the model for this presentation.

Therefore, we've defined three scenarios to propagate through the model: a lower bounds, a most likely, and an upper bounds scenario. The most likely scenario uses averages for uncertain inputs. When considering frequency distributions, we selected the central distribution from the family or curves available. The lower and upper bounds use 10th and 90th percentile values for all uncertain inputs, or the extreme frequency distributions for those cases where a family of curves is available. These boundary scenarios clearly represent a case where our uncertainty is positively and completely correlated, but the interval between the boundaries includes every other possible correlation, including the assumption there is no correlation in our uncertainty.

We modeled ground beef production and consumption from the farm to table. We're dealing with a product that originates from different classes of animals and changes form as it moves from farm to table. Furthermore, the environmental conditions that the products and the 0157 organisms contained within them are exposed to depend on the transportation, storage, and handling of the products.

We modeled two general types of cattle operations. Breeding operations are relatively small. About 20 percent of all cattle slaughtered in the U.S. are culled breeding cattle. On average, we assume that cattle culled from these operations are slaughtered independent of one another.

Feeding operations tend to be larger operations. About 80 percent of the cattle slaughtered in the U.S. are feeding-type cattle. Cattle from these operations are more likely to be shipped to slaughter with others from the same operation and cannot be considered to be slaughtered independent of one another. Cattle in these feedlots are usually shipped in lots of 40-head capacities. We use the 40-head truckload as a basic unit for comparing live cull

and feeder cattle at slaughter.

This is a model output from the production segment of a risk assessment. It is a frequency distribution for the number of culled breeding cattle that are shedding 0157 in their feces. As this graphic shows, the number of shedding culled cattle within a 40-head sample varies. This frequency distribution is the most likely scenario result.

This graph overlays the upper and lower bounds scenarios with the most likely scenario distribution from the previous slide. As these distributions show, the lower bound predicts there are higher frequencies of smaller numbers of infected cattle per 40-head truckload.

This graph shows the same results for feeding cattle. Again, this graph overlays the lower and upper bounds scenarios on the most likely distribution. It is clear from this analysis that there is less uncertainty associated with feeding cattle than breeding cattle.

The slaughter segment of the model comprises two basic types of slaughter plants. We model one plant type that slaughters feeding cattle. Ground beef is a by-product of this model plant type. We also model a plant type that slaughters culled breeding cattle. Ground beef is a primary product of this model plant type.

Overall, about two-thirds of all ground beef in the U.S. is generated from feeding cattle, while the other one-third is generated from culled breeding cattle. For each slaughter plant type model, two forms of meat trimmings are aggregated. Combos are modeled as 2,000-pound aggregates of meat trimmings, while boxes are modeled as 60-pound aggregates.

This chart shows the log of CFUs in contaminated combo bins generated from fed cattle. As you can see, when combo bins are contaminated, they are usually contaminated with relatively low numbers of 0157 bacteria. Note that these represent total organisms in a combo. The concentrations per gram of contaminated combo bin would be quite low since these bins contain about 1 million grams.

Here's the same graph with the upper and lower bounds overlaid. This graph also shows the log CFUs in contaminated combo bins, but these combo bins are generated from culled breeding cattle.

This is the same graph then with the upper and lower bounds overlaid.

Combo bins and boxes of meat trimmings are composed of different ratios of lean to fat. During the mixing and grinding of trim, different numbers of combo bins and/or boxes are combined to generate grinder loads of ground beef. The mixing and grinding of trimmings occurs in large commercial operations or smaller retail settings, and there's a wide variability in how trimmings are combined.

Overall, about 92 percent of ground beef is generated from grinding combo bins of trim. The other 8 percent is generated from grinding boxes of trim or retail trim. Many products are generated from the grinding of meat trimmings. These varied products are also handled in many different ways during distribution and preparation.

The output from the preparation model is an exposure distribution. The most likely exposure curve is shown here. In this graph, the x axis is in log CFUs per contaminated serving, while the y axis is in log number of servings. The shape of the curve suggests that contaminated

servings are most frequently contaminated with small numbers of organisms.

This is the same exposure distribution with the upper and lower bounds overlaid. These boundaries suggest a great deal of uncertainty regarding the true exposure distribution.

This is our last slide in this overview presentation. It summarizes average model output across the three exposure segments. It's a bit busy, so let me explain it.

All of the numbers here are averages. We've weighted breeding and feeding output by the production of cattle and product generated by each of the types. Furthermore, the concentration data is represented in all cases on a per-gram basis. Finally, these results reflect the most likely scenario for the model's outputs.

The bars show the prevalence at each stage. Starting at the left, we see that an average of 11 percent of all live cattle enter slaughter plants shedding 0157 in their feces to some degree. The average prevalence of contaminated carcasses just after dehidng is 4 percent. As we aggregate trim from carcasses into combo bins, we see the prevalence of combo bins with at least one CFU of 0157 in them is 23 percent. As we aggregate combo bins into grinder loads, the average prevalence of contaminated grinders generated from combo bins is 81 percent.

Finally, after preparation and cooking of ground beef meals, the model predicts that about 2 in every 100,000 servings contain one or more 0157 organisms. The line in this graph shows the average log CFUs per gram of contaminated material. Although we don't explicitly model the number of 0157 organisms per gram of feces, we use an average of 2.5 logs from published data here.

On carcasses, the model predicts an average of negative 1.5 logs per gram of trim generated from contaminated carcasses.

As trim from multiple cattle are aggregated into combo bins, the average concentration per gram of combo bin decreases to minus 4.5 logs. Because there is some possibility for multiplication of 0157 within combo bins, the concentration increases slightly in grinder loads.

Finally, because the average serving size is around 100 grams, the concentration per gram of contaminated serving increases to about minus 1 logs, or about 10 0157 organisms per contaminated serving.

Now, this finishes our overview of the model. We'll proceed now directly then to the correlation of model outputs.

DR. SCHLOSSER: I'm Wayne Schlosser from FSIS.

Models should reflect the state of the world to the extent data is available to describe it. Consequently, we attempt to correlate the model output with the state of the world by either anchoring the model to real data within the model or by validating the model with data external to the model. This correlation offers assurance that the model does reflect the state of the world to the extent possible.

Where possible, we've considered the implications of surveillance data within the structure of our model inputs. In some cases, we needed to develop intermediary empiric models to analyze the surveillance data. These empiric models then apply particular inputs for the final

model. Comparison of the model output to real-world data is known as validation. In general, data used to validate the model is not included during construction of the model. This data thus provides an independent benchmark for comparison. In some cases, independent data is not available for validation.

Data for correlation purposes needs to be representative. Fortunately, FSIS has analyzed samples for 0157 from a cross-section of the slaughter and processing industries. For example, year-long baseline studies of carcass contamination were conducted prior to implementing HACCP.

FSIS also routinely collects ground beef samples for 0157 analysis. Recently, a study in Canada was published which surveyed cattle status at the slaughter plant. We compared the implications of these three sources of data with our model outputs for the exposure segment of the model. And, of course, human case number estimates are also available for comparison with our model's predictions. Mark Powell will discuss those comparisons later today.

Whatever the surveillance data might be, it usually needs to be adjusted to account for uncertainty. Point estimates of percent positive will not suffice in describing our confidence in the results. In some cases, we need to account for the sensitivity of methods used. We must also recognize the effect of sample size, both number of samples and the quantity of sample collected in these surveillance data. Therefore, surveillance data is represented in our analysis with attendant uncertainty.

As we mentioned previously, our model output uncertainty is represented by lower and upper bounds. For comparison with surveillance data, we represent modeled output as confidence bars extending from the lower to upper bound, with the most likely output indicated between these extremes.

The first point in the model where data exists for comparison is the frequency of live cattle that are fecal shedders at the slaughter plant. This Van Donkersgoed study was conducted in a Canadian slaughter plant during a one-year period. Since we did not use this data in developing our estimates for the production segment of the model, this comparison can be considered strictly as validation.

Overall, the study found 12 percent of steers and heifers were 0157 positive at slaughter, while 2 percent of culled cows were positive. The study used very sensitive fecal sampling and culturing methods, so a little adjustment for sensitivity was needed to compare these results with the output of the production segment of the model.

This graph compares the uncertainty distribution for the Canadian study's culled cows to the model's output for cows and bulls just before slaughter. The red line represents the range between the upper and lower bounds of the model, with the green diamond representing the most likely value. The blue line is the likelihood distribution for prevalence derived from the Canadian data.

While there is some overlap between this surveillance data in the modeled output, the model is predicting slightly greater prevalence relative to the Canadian study. In this graphic, the Canadian data has been adjusted for test sensitivity, and the relative likelihood of prevalence has been calculated using the binomial

distribution.

This graphic shows how the Canadian data match up with the modeled output for steers and heifers just before slaughter. In this case, the data and the model clearly overlap.

Moving on, we considered the FSIS baseline sampling data collected prior to HACCP implementation. Samples representing three separate areas of approximately 300 square centimeters were collected from carcasses of cow and bulls and steers and heifers. In the steer and heifer baseline study, approximately 0.2 percent of carcasses were positive for 0157. Cow and bull carcasses yielded no positive results.

Enumeration of the positive samples revealed that the most probable number of organisms on the positive sampled areas ranged from 0.03 CFU per cm² to 3 CFUs per cm².

This sampling data was used to construct a simple empiric intermediary model. In this model, we assumed the amount of carcass surface area contaminated could range from 300 square centimeters, the areas sampled in the baseline study, to about 30,000 square centimeters, or the entire surface area of the carcass.

If we assume the entire surface area of the carcass is contaminated, then we would expect that FSIS sampling methods, given the number of bacteria present, would identify 77 percent of all contaminated carcasses. On the other hand, if only 300 square centimeters were contaminated, the sensitivity of the sampling procedure drops to about 25 percent. These bounds on sensitivity thus allow us to predict the prevalence of positive carcasses to be from about 0.25 percent to 0.75 percent.

We next constructed simulated combo bins, each holding trim from 75 cattle. The resultant frequency distribution for contamination in combo bins allowed us to predict the frequency and extent of contamination in grinder loads. The model then simulated ground beef sampling and testing in accordance with the FSIS procedures.

When we tested our upper bound assumption that the entire surface area of the carcass was positive, the model predicted that about 0.14 percent of 25-gram samples would be positive and about 1.4 percent of 325-gram samples would be positive. FSIS ground beef sampling data for 1995 through 1997, however, yielded only 0.08 percent positive 25-gram ground beef samples. In 1998, with a larger sample size of 325 grams, FSIS found 0.33 percent of ground beef samples positive, still well below the upper bound predicted by the model.

The lower bound assumption of 300 square centimeters of contaminated area significantly underpredicted the number of positive samples that would be found. Thus, a value for contaminated surface area somewhere between these extremes seemed likely.

When we assume a contaminated surface area of 3,000 square centimeters, which is the log midpoint between assuming the entire surface area is contaminated, and assuming only 300 square centimeters are contaminated, the predicted number of positive ground beef sample is consistent with both the 25-gram and 325-gram sample size results reported by FSIS. Thus, we anchor the contaminated surface area in our full slaughter model at 3,000 square

centimeters. So let's look at the output generated from that slaughter model.

This chart compares the prevalence of positive carcasses from cows and bulls predicted by the model with FSIS sampling data. The dark blue line represents the likelihood of different prevalence levels, given the sampling data. The model tends to slightly overpredict the number of positive carcasses when compared to the sampling data. Please note that the range of uncertainty from the model is due to the cumulative effect of all the uncertain inputs that contribute to this output as well as the method we are using to communicate our uncertainty.

This chart is similar to the previous one, except steers and heifers are compared, and as in the previous chart, the model tends to slightly overpredict compared with FSIS sampling data.

As you saw earlier, we used FSIS ground beef sampling data in constructing our intermediary models. From 1995 through 1997, FSIS used a sample size of 25 grams to represent a grinder load and found four positive samples out of 4,999 collected. In 1998, FSIS began using a sample size of 325 grams and found 12 positive samples out of 3,597 collected.

This chart shows the overlap of ground beef sampling predicted by the model with the actual likelihoods calculated from FSIS testing of 25-gram samples.

This chart shows the same overlap for 325-gram samples.

In conclusion, the model is anchored in observed data as we look at live cattle, carcasses in the slaughter plant, and samples of ground beef leaving the grinder. Unfortunately, there is no data available that directly measures the number of humans that are actually exposed to 0157 from ground beef. Also, as we noted, the model output boundaries tended to be wider than the confidence limits of the data. This is to be expected considering all of the uncertain inputs to our model and the type of uncertainty analysis performed. This analysis propagates increasing uncertainty as we progress from farm to table.

We'd be glad to answer any questions you might have regarding both the correlation analysis and the overview.

DR. GILL: Colin Gill, Agriculture Canada. Aren't the observed data numbers so small that you can't really make any correlation at all between your model and the observed numbers? I mean, if somebody licked their finger, you would get--it would throw your correlations right out.

DR. SCHLOSSER: Well, we didn't think so.

DR. EBEL: Which data are you talking about?

DR. GILL: The number of positive samples in the observed data are so small that I can't see how you can correlate anything with your model.

DR. EBEL: Is that concerning carcasses or ground beef or--

DR. GILL: The whole lot.

DR. EBEL: --or all of it?

DR. GILL: All of it.

DR. EBEL: Well, the data is what the data is.

Certainly, as--data increases your confidence in what the data is saying is narrowing down and certainly suggesting higher likelihood in the implied prevalence or

concentration, or whatever it is we're measuring, but it certainly reflects what those results were and the distributions in terms of the uncertainty are reflected, I mean, as objectively as we can reflect them. To add increased uncertainty beyond what the data implies doesn't seem warranted in this case.

MS. OLIVER: Dane?

DR. BERNARD: Thank you. Dane Bernard.

Your consideration was fed cattle, steers and heifers, and culled breeders, and I'm not a professional in the beef industry by any measure, but I expected some culled dairy animals possibly to be included. Is this not a significant portion of meat that goes into ground beef comes from culled dairy animals, or am I mistaken there?

DR. SCHLOSSER: We've included both culled dairy and culled beef animals in the breeders.

DR. BERNARD: Okay. And another question. The Canadian study that you referred to, that study also included culled animals? Was it targeted to culled animals? Because I noticed you compared the outputs from the Canadian study with the calculations that you'd made on culled animals in the States.

DR. EBEL: They actually stratified their results based on culled breeding cattle and feeding cattle. So we actually have those results summarized. I don't know if we can page up to that. Maybe we can.

Those results there at the bottom of that slide are the reported results from the Canadian study, so 12 out of 593 culled cattle were sampled and found positive.

DR. BERNARD: Not to roll back the clock two days, but I just wanted to make sure we're comparing apples to apples here.

In addition, I'm assuming that the cattle that would have been in the Canadian study would have come from a climate somewhat northern than most of the cattle that would be in the U.S. study. I have seen papers that seemed to relate geographic areas with prevalence of certain pathogens and related to climate. Is there an effect there that should be compensated for or considered? I notice we had, you know, some uncomfortably large uncertainty bars there, and, again, I'm not a professional with that, but I'm wondering how much might be due to factors that may not have been compensated for.

Thanks.

MS. OLIVER: Jim? And if I could ask the presenters when you're speaking, since you have two of you, to identify yourself before giving responses. Thank you.

DR. DICKSON: Jim Dickson, Iowa State University. I think it's a general question. Is this information, are these graphs available on your Web page? Because I had some specific questions on the data which I'd really--I'd like to have the graphs in front of me rather than trying to watch them on the screen as they go by. Is there an opportunity to see all this on your Web page or where would we get copies of this?

DR. POWELL: When the draft report is produced, we'll place that on the Web page, and a copy will be submitted to the docket. This is Mark Powell responding.

DR. DICKSON: But as we sit here today, there's not an opportunity to get a hard copy of this, then?

DR. EBEL: Do we have a hard copy of this

presentation available?

DR. POWELL: Do we have the capability to do that, Karen?

DR. HULEBAK: I think you do, yes.

DR. POWELL: Yes, we'll have the disk taken over and get hard copies made.

DR. DICKSON: It doesn't necessarily have to be today, but if we could get copies of it for--

DR. HULEBAK: Okay, sure. Any one of you who wants more information, which is absolutely available, about any section of this discussion today, let us know and we'll send it to you forthwith.

DR. DICKSON: Okay. Thank you very much.

DR. HULEBAK: I'd also like to acknowledge the recent arrival of Dr. Chuck Haas, Drexel University, and Dr. John Kobayashi.

MS. OLIVER: Thank you. Mike Doyle?

DR. DOYLE: Mike Doyle, University of Georgia. I'm a bit unclear as to where you come up with some of these numbers. For example, you've got 11 percent of the cattle shedding E. coli 0157. What's the basis for that?

DR. EBEL: Well, I guess, as we started off, we are going to be presenting each of the segments of the model in sequence, but we wanted to give sort of the results up front, and we hope that some of these distributions will become clearer as the day goes on in terms of how they were derived.

DR. DOYLE: All right. I'll wait. Thank you.

MS. OLIVER: Skip?

MR. SEWARD: Skip Seward, McDonald's. If I read your one slide correctly on the combos when you were predicting contamination levels, then your comparison on that was to data which you had for ground beef. Is that because--if I saw that correctly, is that because you just didn't have data on combo contamination and that's why you used that as a comparison?

DR. EBEL: Yes, we don't have any data available that represents a good cross-section of combo bins. The comparison was actually at the grinder load levels, which, you know, represents an aggregate, and each grinder represents two or more combo bins that have been combined to be ground. So the actual comparison is at the grinder load level.

MR. SEWARD: So your levels would be higher there based on what you showed earlier.

DR. EBEL: Right. The prevalence of contaminated grinder loads is higher than the prevalence of contaminated combo bins coming out of our model. But the actual sample--the comparison is really at a sample level, a sample taken from a grinder load, what's the likelihood of it being positive, which incorporates both the prevalence of contaminated grinder loads, but also how many organisms are in there that are even available to be detected. So as you see from this, the raw prevalence data suggests very low frequencies of draws would be contaminated based on just going out and randomly sampling contaminated--or across the population of grinder loads.

MR. SEWARD: Thank you.

MS. OLIVER: Mike Jahncke?

DR. JAHNCKE: Mike Jahncke, Virginia Tech.

Getting back to a comment that Dane made, is there

any attempt here to split out your culled dairy from your culled cattle, or are they lumped together?

MS. OLIVER: Can you please identify yourself again for the record?

DR. EBEL: Eric Ebel. We'll go into that in the production segment, but just to say that we did not separate dairy from beef cow/calf cull animals. We considered them combined because that's typically how they're managed at the slaughter plant level, and statistics are available at that level of aggregation. So we haven't separated dairy from beef industry cull animal, but consider them together.

DR. JAHNCKE: Is there a possibility at some point that you can split those out, or is it just a function of insufficient data to be able to split them out?

DR. EBEL: I guess that's a justification at this point. We don't have very much evidence on the beef cow/calf side. As we get into the production segment, hopefully some of that evidence will come out.

DR. JAHNCKE: Thank you.

MS. OLIVER: Swami?

DR. SWAMINATHAN: Bala Swaminathan, CDC. I just needed a clarification.

On the comparison of the Canadian surveillance data with the model output, the model prediction was higher than what the surveillance data indicated, and you made a statement--also the Canadian study apparently used a more sensitive method. You made a statement that the Canadian data were adjusted for test sensitivity. Could you clarify that, please?

DR. EBEL: We adjusted for the sensitivity, but we did want to point out that the methods that were used up there represent more sensitive methods than have been used maybe--I don't want to say "traditionally"--I'm sorry, again, Eric Ebel--have been used traditionally, but we still needed to adjust that data because what we're trying to represent in the model would be what we would call a true prevalence of, you know, cattle that are shedding 0157 organisms, and the data that is presented on the Canadian research still is going to have some false negative results in there. So we wanted to adjust for that, and I believe we used a sensitivity of 96 percent, so that 96 out of every 100 infected cattle would actually be detected in the Canadian study based on that assumed test sensitivity. But we still needed to make that adjustment as we made the comparison.

DR. ROSE: Bonnie Rose, FSIS.

Wayne, for the 1992 to '94 steer heifer and cow/bull baseline studies, did you indicate that the sample size was 300 square centimeters, or did I hear that correctly?

DR. SCHLOSSER: Three separate areas of 300 square centimeters.

DR. ROSE: I believe the total area sampled was 60 square centimeters by the excision method, 20 square centimeters at each site.

DR. SCHLOSSER: Okay.

DR. ROSE: The actual analytical unit was 60 square centimeters.

DR. EBEL: Yeah, sample area sampled.

MS. OLIVER: Mike?

DR. ROBACH: Mike Robach, Conti Group.

My question also relates to the sampling, and I was wondering when you were considering the 300 centimeters versus the whole carcass assumptions, were you looking at the 300 centimeters randomly or was this a site-directed sample?

DR. EBEL: Eric Ebel. We assumed basically a random sample in our analytic approach. We didn't use a targeted approach, obviously. In the baseline study there were targeted areas that were actually samples, so this was a simplification in our analysis that we made.

DR. ROBACH: Well, just so I understand, so the 300 square centimeter sample in the model would have been a random 300-centimeter site; is that correct?

DR. EBEL: Right, times three.

DR. ROBACH: Times three.

MS. OLIVER: Are there any other questions? Leon.

DR. RUSSELL: Leon Russell, Texas A&M University.

You mentioned early prevalence of fecal shedders per year. How was that data collected? Was that purely prevalence or was that cumulative incidents?

DR. EBEL: I believe the context--this is Eric Ebel--the context that was in the example of uncertainty, that if we could know what the prevalence of fecal shedders across all slaughter plants in the US that are killed in a given year, you know, we would obviously need to sample with 100 percent accuracy, but whatever estimate we get we're going to have some uncertainty about that number. We haven't measured--and as far as I know, nobody has measured prevalence of fecal shedding in cattle across all slaughter plants in the US, but at some point, when that data becomes available, there will be attendant uncertainty simply because we can't sample all the cattle, and as a consequence, any estimate has some measurement error in it.

DR. RUSSELL: Thank you.

MS. OLIVER: Peggy.

DR. NEILL: Peggy Neill.

I'm not sure if I should direct the question to you all or to the Committee at large. Is cattle slaughter equally distributed or equally frequently conducted across all months of the year? Because I think you can see where I'm going, is that if cattle slaughter does not occur equally across months of the year, and frequency of fecal shedding is not equal across months of the year, then the model might have to take that into account.

DR. EBEL: Well, we'd be glad for somebody else to comment. As far as we know, we believe that in general there's a uniformity. Certainly within the culled breeding cattle part of it, there's some seasonality or cycles that go on as a result of seasonal patterns in breeding and so forth, but in general, we would believe that the cattle slaughtered on a monthly basis are relatively constant, as far as we can remember.

MS. OLIVER: Dan, do you have a response to that?

DR. ENGELJOHN: Dan Engeljohn, USDA.

Yes, I would say that it is reasonably uniform throughout the year, and we certainly have access to that information, so we can come up with it.

Can I follow up with a question?

MS. OLIVER: Sure.

DR. ENGELJOHN: I think this is directed towards

Wayne.

You had made a statement that with regard to the combo bins, that contained 75 cattle or the product of 75 cattle. I'm just curious. Is that something that you knew or is that an assumption that you had made?

DR. SCHLOSSER: That was an assumption just for that basic model that we used, trying to correlate as we were going along. As we go into the slaughter model you'll see that we have a range to that, varying from just a few cattle if it's cows and bulls, to perhaps more cattle than that if it's steers and heifers.

DR. ENGELJOHN: This is Dan Engeljohn, the follow up.

Just to let you know, we do have information, or we have received information about what is expected to be in a combo bin in terms of what that represents, so I'm curious to hear what you have to say later.

DR. POWELL: This is Mark Powell. And again, I'd just like to follow up that the intermediate empiric model that Wayne presented was simply designed to try and get our best estimate for the surface area that would be contaminated on a carcass between the bounding estimates. Okay. So it is an input into the slaughter model, and the model that Wayne elaborated was simply designed to identify the most likely within those bounds as an input, not as an output to the model.

MS. OLIVER: Thank you. With that, we'll take a 15-minute break and come back at about 9:35. Thank you.

[Break from 9:16 a.m. to 9:38 a.m.]

MS. OLIVER: The first thing I would like to announce is that we didn't say anything about public comment before, and the agenda didn't have anything, but if somebody wants to sign up for public comment, we'll have an opportunity for that later. You can sign up at the desk here or at the table outside, and we'll allow that. We'll see how many people sign up and find an opportunity for that.

Our next presenter is --

DR. EBEL: Eric Ebel.

MS. OLIVER: Right, Eric Ebel on production and Karen Hulebak is going to introduce the section on the questions that FSIS wants answered.

DR. HULEBAK: Thanks, Janice.

Just to reiterate, as you listen to this section on production, keep in mind the following two questions. Can you, the Committee, recommend a better way to link live cattle to contaminated carcasses? And second: Are there data or methods currently available that would improve the quantitative links among fecal, hide and carcass contamination?

DR. POWELL: This is Mark Powell.

I have a housekeeping comment, and that is that there have been some typos and other modifications made to the handouts that were sent out to you earlier. We apologize for that, but we will get a final set to you of what is presented on the screen. I don't think there should be any problem following the rest--the remainder of today's presentations, and we will be submitting the final copy to the docket and distributing it to the Committee and the invited experts.

MS. OLIVER: Thank you.

I'd just like to make one more announcement, and

that is that Paul Mead and Nancy Strockbine from CDC have now joined us as the invited experts, so welcome.

And now we'll continue on with Eric Ebel. Excuse me. Jim Dickson had a question. I'm sorry.

DR. DICKSON: This is just a general comment. Jim Dickson at Iowa State.

I don't know how the rest of the Committee feels, but I would be more than happy to take these in electronic format, as opposed to getting another stack of handouts to take home or carry with me in the mail.

MS. OLIVER: Sure.

DR. POWELL: Thank you. And we can accommodate that. We have it electronically available in PowerPoint format. For those of you that operate in another environment, I apologize. We would be more than glad to send the data electronically. It's much easier on us. So, yes, we'll do that, we'll send them electronically, and if you could just let the Secretariat know if that's going to be inconvenient for you, and we can make arrangements to have them sent via hard copy.

MS. OLIVER: Right. I think that's best. We'll send--our default will be to send electronically. If you want hard copy, please let me know. Okay.

DR. EBEL: Thank you.

Undoubtedly 0157 contaminated or infected cattle entering the slaughter process influence the contamination of ground beef. Yet, our understanding of a quantitative association between incoming status of slaughter cattle and outgoing status of meat harvested from the cattle is limited.

At this point the quantitative link between pre-harvest and post-harvest contamination is only established for those cattle that are fecal shedders of 0157, and that link is tentative. Consequently, we will limit our modeling of live cattle status to fecal shedding. We expect that data linking hide contamination to carcass contamination is forthcoming, however.

The production segment is the first part of a farm-to-table model. Its purpose is to simulate the proportion of live cattle at slaughter that are 0157 infected.

There's a lot of data pertaining to the occurrence of 0157 in live cattle. Therefore, our challenge in this segment is to coalesce this sometimes conflicting evidence into a cohesive picture of what we think the true occurrence is. I will present information on the development of the production model and the data used to estimate its variables. I will also present some provisional results, as well as discuss data gaps for this model that could be filled through additional research.

The 0157 Process Risk Model--doesn't want to stay up, does it--they say the process risk model begins where the production of beef begins, at the farm. Most of the information available on the occurrence and distribution of this organism in US livestock has been collected during surveys of farms and feedlots.

Many risk factors hypothesized to influence 0157 status in cattle are factors that apply to whole herds. An important reason for incorporating the farm in the process risk model is that reductions in the prevalence of affected cattle entering slaughter plants will be accomplished

through actions on the farm or feedlot.

The production segment separated culled breeding cattle from feeding cattle. We do this because the slaughter, processing and distribution of meat from these types of cattle is different. Feeding cattle are defined as cattle sent to slaughter from feedlots. Typically, these cattle are steers and heifers. Steers and heifers comprise about 80 percent of all cattle slaughtered in the US annually. Culled breeding cattle are defined as cattle sent to slaughter from dairy or beef cow calf herds. These cattle are typically mature cows or bulls. Cows and bulls comprise about 20 percent of all cattle slaughtered in the US annually.

The three general states of the production segment are: on-farm, transportation and slaughter plant. The on-farm stage estimates the within-herd prevalence of 0157 infected cattle and the herd prevalence of 0157 affected herds. In the transportation stage we considered the effect of transit time and commingling on the transmission and amplification of 0157 infections. Yet, all the observational evidence suggests that there is no substantial difference in fecal prevalence between the farm or feedlot and the slaughter plant. Therefore, we model no change in prevalence between the farm or feedlot and the slaughter plant. In the slaughter plant stage we consider the effect of cattle clustering as they enter the slaughter plant.

Whether they originate from feedlots or breeding herds, cattle destined for slaughter must be shipped to a slaughter plant. During shipment transmission of 0157 may theoretically occur. Alternatively, some infected cattle may clear their infection during shipment. The available evidence shown here does not imply there are dramatic differences in fecal prevalence between the farm and slaughter plant. Transit between the farm and slaughter plant may not affect prevalence of infected cattle, but it may be important in causing changes in hide prevalence. Studies of hide contamination with Salmonella suggests an increase in prevalence of hide contaminated cattle between the farm and slaughter. Unfortunately, there is no data on 0157 hide contaminated cattle at the farm, and only limited data concerning hide prevalence at the slaughter plant. Therefore, inclusion of the effect of transit time on hide contamination in this model awaits the availability of such data.

Culled dairy and beef cows and bulls arrive at the slaughter plant from their farms of origin after transit on trucks. The majority of these cattle arrive after first being shipped to one or more livestock markets, where they are auctioned to the highest bidder, then shipped to slaughter. The combined average herd size for beef and dairy herds is approximately 300 cows. According to survey statistics, approximately 25 percent of cows in dairy herds and 11 percent in beef hers are culled each year. These culling percentages imply that the average herd would market about 1 to 1-1/2 cattle per week. Given the low number of cattle contributed per herd and the commingling of cattle in livestock markets, it is reasonable to assume random mixing of culled breeding cattle at slaughter plants. Such an assumption implies that the probability of infection is independent between cows at slaughter.

Output from the production segment is generated

using Monte Carlo simulation techniques. For culled breeding cattle we simulate the number of infected cows and bulls in a group of 40 such animals that would be presented for slaughter. We use 40 head as a convenient count because that's the capacity of most trucks that are used to haul cattle to slaughter. Each cow and bull is simulated as an individual. The probability of infection is equal to the product of herd prevalence and within-herd prevalence. Within-herd prevalence varies according to an exponential distribution. The only parameter in the exponential distribution is the mean within-herd prevalence among all infected herds.

Simulation of the production segment, when herd prevalence and within-herd prevalence are set at their lower, most likely, and upper bounds, produces the three output distributions shown here. This output feed in to the slaughter segment. Each of these distributions explain the number of--that the number of fecal-shedding cattle varies in any group of 40 head. On certainty regarding the true distribution is reflected by the three different distributions.

Looking at the most likely distribution, the middle one of those three, the underlying true prevalence is 4 percent. For the lower-bound distribution the underlying true prevalence is 3 percent. For the upper-bound distribution the underlying true prevalence is 6 percent.

Greater than 90 percent of steers and heifers are shipped directly from feedlots to slaughter plants without going through livestock markets. Furthermore, these cattle are usually slaughtered together in a lot, although they may be mixed with one or more truckloads of cattle from the same or another feedlot. The manner by which feedlot cattle are marketed suggests they are more likely to be processed at the slaughter plant in a clustered pattern. Clustering implies that the infection status of a steer or heifer in a slaughter plant is dependent on the lot it is in.

If we simulate the number of infected cattle per truckload using the equation shown here, each truckload is independently determined to be from an affected or non-affected feedlot based on the herd prevalence. If the truck is from an affected feedlot, then the number infected in the truckload is determined based on the within-herd prevalence. Again, within-herd prevalence varies according to the exponential distribution.

This figure is the output for infected steers or heifers in a truckload of 40 such animals presented for slaughter. Upper and lower bounds result from uncertainty regarding within feedlot and feedlot prevalence. In contrast to the distribution for breeding cattle, this distribution is skewed. It's most-likely value is zero infected cattle in a truckload. Zero cattle can result either because the truck originates from a non-affected feedlot, or given that the truck originates from an affected feedlot because the sample of 40 head from that feedlot failed to contain any infected cattle.

Looking at the most likely distribution in this graph, the underlying true prevalence of fecal shedders is 13 percent. For the upper and lower-bound distributions, the underlying true prevalence of fecal shedders are 11 and 16 percent, respectively.

Herd or feedlot prevalence is assumed to be a

fixed but uncertain input to the production segment. In other words, we assume there is some steady-state proportion of herds at any given time that are affected. The lack of evidence suggesting there are changes in the proportion of the affected herds in the US over time supports this assumption.

Seasonal changes in herd prevalence have been reported, but these changes are probably the result of seasonal changes in the within-herd prevalence for infected herds. Herd or feedlot prevalence is a function of herd sensitivity and the sampling data. Herd sensitivity is the proportion of herds that test positive given the number of samples collected per herd and the apparent within-herd prevalence.

We used 5 studies to estimate the prevalence of infected breeding herds. These studies were selected because sampling was conducted across multiple states. National studies on the occurrence of 0157 in breeding herds have not shown any differences in prevalence between regions of the country. Therefore, inferences drawn from the selected studies are thought to be representative of US breeding herd prevalence.

The Garber study is the largest study. It was part of a national survey of the US dairy industry conducted by the USDA. This survey collected fecal samples from 91 dairy herds across the US. Sampling was stratified for herd size. To account for seasonal bias in sampling and differences in sample size, we separately analyzed large and small herd results from the survey.

The Hancock studies sampled dairy herds across three northwestern states. In general, several monthly sampling visits to each herd over 3, 6, or 12 months, were made in these studies.

The final studies samples 15 cow/calf beef herds across 5 midwestern states. This study was completed by USDA-ARS researchers. In each herd 60 fecal samples from weaned calves were collected.

The prevalence of affected feedlots is estimated using these three studies. These studies include feedlots that were sampled from multiple states. Because the occurrence of 0157 in feedlots is assumed to not be geographically clustered, inferences drawn from these studies are also considered representative of the US feedlot prevalence.

The largest study of 0157 occurrence in US feedlots was conducted by USDA and reported by Dargatz. In this study 100 feedlots with greater than a thousand-head capacity were randomly selected throughout the US. In each feedlot 120 fecal samples were collected for a determination of apparent prevalence.

Another survey of 6 feedlots in Idaho, Oregon and Washington was completed by Hancock. On average 180 samples were collected from each feedlot.

Smith has recently reported results from intensively sampling 5 midwestern feedlots. Over 600 fecal samples were collected in each of these feedlots.

Herd prevalence is dependent on herd sensitivity. We calculated herd sensitivity based on apparent within-herd prevalence and the number of samples collected per herd. In this figure p stands for the apparent within-herd prevalence variable, and n stands for the average number of sample

collected in each herd. As implied by this equation, herd sensitivity equals 1 minus the average or expected value of the probability that no infected cattle would be detected in a sample of n cattle. A herd sensitivity was calculated for each of the studies we analyzed.

The herd and feedlot prevalent sampling evidence implies apparent herd prevalence. To estimate the true herd prevalence we used base theorem, which is the top equation shown here. The likelihood function in base theorem is the equation at the bottom of this slide. It shows that the likelihood of herd prevalence is a function of the sampling evidence and the herd sensitivity.

We derived these likelihood distributions for the 5 studies concerning herd prevalence. The Garber study was stratified so there was actually 6 curves in this figure. For each study the likelihood distribution reflects uncertainty in true herd prevalence. Again, this uncertainty is driven by the number of herd sampled in each study, the number found positive, and the herd sensitivity. The broadest and therefore more uncertain likelihood distribution is that for the distribution labeled "1a." This broad distribution results because herd sensitivity in this case was calculated at 21 percent, which is so low that a wide range of true herd prevalence levels are nearly equivalently feasible. In contrast, the other curves reflect increased certainty regarding herd prevalence levels because herd sensitivity was much larger, ranging from 76 to 96 percent in these other studies.

The 5 likelihood distributions from the previous slide are combined using base theorem. The resulting distribution for herd prevalence is shown here. For our most likely scenario, herd prevalence was set equal to the expected value or average of this distribution. For the upper and lower-bound scenarios, herd prevalence is equal to the 90th or 10th percentiles of this distribution.

Likelihood distributions were also derived for the three feedlot studies. In this analysis the herd sensitivity was calculated as 77 percent, 86 percent and 99 percent for the Dargatz, Hancock and Smith studies, respectively.

The Dargatz study's likelihood curve suggests the most likely feedlot prevalence is somewhere around 85 to 90 percent. The other two studies, which sampled only 5 or 6 feedlots, suggest that the feedlot prevalence is most likely around 100 percent.

The three likelihood distributions for feedlot prevalence are also combined to from the distribution shown here. Again, the most likely feedlot prevalence was set equal to the average of this distribution. Upper and lower-bound scenarios used feedlot prevalence levels equal to the 10th and 90th percentiles of this distribution.

Cattle sent to slaughter represent a special subset of their respective herd populations. For example, a cow culled from a dairy or beef herd may have a different probability of being infected than a calf in that same herd, or the prevalence of 0157-infected cattle about to be sent to slaughter from a feedlot may be different from the prevalence in cattle that have just been assembled to begin feeding in that feedlot. In general, the research suggests that there is a declining prevalence of cattle infection with increasing age of cattle.

In our model we applied the within-herd prevalence evidence that is most specific to cattle being sent to slaughter. True within- or feedlot prevalence, is a function of the sensitivity of the test used to diagnose fecal shedding of individuals, as well as the apparent prevalence observed in our studies that were presented.

The average breeding herd size is about 300 cows per herd. Therefore, we assume a lower limit to within-herd prevalence of one infected cow in 300. As a conceptual model of 0157 infection in cattle herds, we assumed infected cattle are colonized for a defined period. Research has shown that a carrier state for 0157 in cattle is unlikely. Nevertheless, there is evidence suggesting that cattle are susceptible to reinfection following clearance of colonization, and that cattle can be infected with one or more strains of 0157 concurrently.

The average capacity of US feedlots is about 6,000 cattle per feedlot. Therefore, we assume the lower limit of within-feedlot prevalence is one infected steer or heifer in 6,000. Additional assumptions introduced for breeding herds also apply to feeding herds.

We used four studies to estimate the average within-herd prevalence of infected breeding cattle in US herds. These studies varied in their design, sampling and laboratory methods. In combination, these studies' results are assumed to represent a cross-sectional seasonally average set of evidence for within-herd prevalence in US breeding herds.

The Garber study was the USDA survey of the dairy industry in which 22 positive herds were detected. The Besser study was a year-long monitoring of 10 dairy herds in Washington. Sampling detected 3 cow herds as infected in that study. The Rice study took a convenient sample of cows about to be culled from dairy herds enrolled in an Idaho, Oregon and Washington survey. And the last study was a survey of 25 cow/calf herds conducted by Hancock in Washington, of which four were positive.

Four studies were used to estimate within-feedlot prevalence. The first study was conducted by USDA and 63 positive feedlots were detected. That study was reported by Dargatz. In a study of fecal prevalence in steers and heifers at four slaughter plants, Hancock reported finding 5.8 percent of 240 cattle positive when sampling was done just after the cattle were stunned in the slaughter plant. In another study of feedlots in three northwestern states, Hancock found all 6 feedlots sampled to contain at least 1 positive steer or heifer. These first three studies used the same lab methods, and the most likely test sensitivity was assumed to be 58 percent.

In the final study, Smith evaluated 5 midwestern feedlots and found them all to contain a high proportion of infected cattle. This study collected more samples in each feedlot, collected larger samples of feces, and used a more sensitive laboratory technique than the other three studies. Test sensitivity was assumed to be 96 percent for this study.

Within-herd prevalence varies from one infected herd to the next. Furthermore, if we were to follow one infected herd over the course of several months, we would find that the prevalence of infected cattle within that herd would vary.

The top graph of this slide is a histogram of apparent within-herd prevalence from a study of post-weaned heifers in 36 dairy herds. This graph implies an asymmetric distribution for within-herd prevalence with the mode equal to the lowest detectible level. Such a distribution shape is consistent with a variable that fits in exponential distribution. In the bottom figure the cumulative probability distribution for this data and that predicted by the exponential distribution are compared. A chi square goodness of fit statistics supports the hypothesis that the data conform to an exponential distribution.

In a national survey of milk cows and culled cows in the US conducted by Garber, 22 infected herds were infected. The cumulative probability distribution for within-herd prevalence is depicted in this graphic. In this case, goodness of fit analysis also supports the hypothesis that these data fit an exponential distribution. The exponential distribution has only one parameter, the mean or average. By assuming that within-herd and within-feedlot prevalence can be modeled using an exponential distribution, we are left with the less difficult task of estimating the average within-herd prevalence from the available data.

The preceding tables of data report apparent within-herd or within-feedlot prevalence. To estimate a distribution for the average, we used a method similar to that already presented for herd prevalence. The only difference for within-herd prevalence is that we used test sensitivity, rather than herd sensitivity in the likelihood function.

Lab methods varied between studies because of different quantities of feces analyzed, different enrichment broths, and different culture media used. Sanderson evaluated lab methods and relative sensitivities were presented. In this table we've interpolated and extended Sanderson's results to incorporate methods not directly studied in that study.

We used these results to model test sensitivity in our analysis. Uncertainty regarding test sensitivity was incorporated by inserting these data into a beta distribution. We used the 10th and 90th percentiles from these beta distributions as the lower and upper-bounds of test sensitivity for the corresponding boundary analysis. We took the means of these distributions for our most-likely estimate of test sensitivity.

Test sensitivity is a function of lab methods and the quantity of sample collected. To evaluate the Sanderson sensitivity data further, we performed the analysis shown here. In the two left-hand columns are displayed fecal concentrations and their estimated frequencies among known infected cattle. The three right-hand columns display the probability that fecal samples of varying sizes would not contain any organisms for the given fecal concentration. At the very bottom of each of these columns then is the probability that a sample of a given size would contain one or more 0157 organisms.

From the Sanderson results we can compare the relative sensitivity for the 0.1 and the 10-gram samples, where the enrichment and plating media--the same enrichment and plating media were used. For 10-gram samples 79 percent of 24 positive cattle were found positive. Yet from the analysis shown here, we expect 95.7 percent of samples from

infected cattle would contain at least one organism if 10-gram samples were collected.

But by dividing 79 percent by 95.7 percent, we find that this enrichment and plating media correctly found 83 percent of the samples containing at least one organism to be positive. Similarly, for 0.1-gram samples, Sanderson says that 58 percent of positive cattle were detected using that sample size. Yet only 73.3 percent of positive fecal samples would contain one or more organisms with that sample. Therefore, 79 percent of the samples with one or more organisms were in fact detected.

The reported sensitivity for this culturing system is 80 percent for experimentally inoculated samples, that the relative sensitivities measured for 0.1-gram and 10-gram samples are consistent with this sensitivity after adjustment for the probability that a sample contains at least one organism is reassuring, in that it suggests that the differences in relative sensitivity reported by Sanderson for naturally-infected cattle incorporate the effect of some samples not containing any organisms. Therefore, we determined that no adjustments to the Sanderson data seem necessary.

We derived these likelihood distributions for the four studies of within-breeding-herd prevalence. The likelihood distributions displayed here assume that the test sensitivity is the average for the size of sample and lab methods used in each study.

The likelihood distributions for the Garber and Besser study are not much different. The Rice and Hancock studies represent small data sets, and their likelihood distribution suggests higher average within-herd prevalence. The Hancock study cited here used the least sensitive sampling methods, which increases the likelihood that many test-negative cattle were theoretically infected.

The middle curve in this graph showed the uncertainty regarding average within herd--breeding-herd prevalence for culled breeding cattle in the most-likely case. It was derived by combining the four likelihood distributions from the previous slide. Lower and upper-bound distributions were constructed similarly by changing the test sensitivity for each study. The expected values of these three distributions were used as the average within-herd prevalence in the three scenarios we modeled.

We derived these likelihood distributions for true within-feedlot prevalence for each of the four feedlot studies. The outlier here is the Smith study. This study includes a substantial amount of data. Consequently, this likelihood distribution strongly influences our estimated distribution for average within-feedlot prevalence.

The middle curve here is the most likely distribution for average within-feedlot prevalence. It was derived by combining the four likelihood distributions on the previous slide. The upper and lower-bounds distributions were similarly derived after changing the test sensitivity. The expected values for each of these distributions were used as the most likely and lower and upper-bounds for average within-feedlot prevalence.

Statistics concerning the uncertain parameters of this model are then summarized here. We estimate that the great majority of breeding herds and feedlots contain at least 0157-infected cattle. As you can see, herd

prevalence, our most likely estimate is 72 percent. For feeding-herd prevalence, it's 88 percent.

DR. HULEBAK: Excuse me. If you're having trouble following, it should be on page 19 of your handout.

DR. EBEL: We estimate that the great majority of breeding herds contain at least 1 infected cattle. Also, average within-feedlot prevalence is over twice as great as average within-breeding-herd prevalence, a result which may support that as cattle age, their likelihood of infection does decline.

A quantitative link between prevalence of 0157 in live cattle and the occurrence of contamination on carcasses or in ground beef is limited. We are aware of only one study, conducted in Great Britain, which has managed to show an association between live cattle status and carcass status for 0157. This study involved a limited number of animals and much uncertainty attends its results.

Therefore, we believe quantifying the connection between live cattle and carcass status is a critical research need. The necessary research will serve to clarify the importance of pre-harvest control in this food safety problem.

The available evidence on the occurrence of 0157 in US cattle is substantial, but still limited. Moreover, the results of studies on the occurrence and distribution of this organism are in some cases different. The approach we've used in handling this data is to incorporate uncertainty about prevalence within each individual study and between different studies. Additional uncertainty regarding herd prevalence enters our model through sensitivity parameters. These three elements of uncertainty, within-herd, between study and sensitivity combine to demonstrate our lack of complete comprehension of 0157 occurrence in US cattle populations.

Uncertainly regarding prevalence could be reduced through additional large surveys of dairy cow/calf and feeding herds. These additional surveys could improve on those surveys cited here by increased sample sizes to account for the low within-herd prevalence levels and quantification of concentrations of 0157 in positive samples to explain the levels of shedding detected. Nevertheless, it is expected there will always be some uncertainty regarding prevalence because definitive field surveys are expensive and difficult to perform.

A great deal of speculation surrounds the role of contaminated hides in the contamination of carcasses with 0157. Very little data is available on the proportion of cattle whose hides are 0157-contaminated, and the concentration of organisms on those hides. The reliability and sensitivity of hide-testing methods needs to be researched. Studies should also explore possible changes in hide prevalence during transportation from the farm to slaughter. Research on Salmonella has suggested that prevalence increases dramatically during transportation. Research is also needed on possible risk factors associated with high contamination. Pen and/or housing design, environmental sanitation practices and feed management are all possible correlates.

There's considerable uncertainty regarding the prevalence of cattle whose hides are contaminated with 0157. In one study 1.7 percent of 240 feedlot cattle at four

slaughter plants had hair samples that were 0157 positive. Paired fecal samples were collected from the animals in this study, and no correspondence between fecal and hide status was found.

Some researchers have hypothesized that the degree of visible soiling of cattle hides or hair with mud, manure, and/or bedding is correlated with microbial contamination of carcasses, but this research has shown that the concentration of generic E. coli organisms on carcasses changes very little, whether the lot was composed of cattle that had substantial hide soiling or the cattle were relatively clean. The implication of this research is that the role of 0157 hide contamination and carcass contamination may not be correlated with visible clues. Nevertheless, there is some indication in the research that wetter cattle may result in carcasses with greater levels of contamination.

Many studies of 0157 have tested the association of hypothetical risk factors with the occurrence of 0157-infected cattle. These studies have furthered our understanding of the epidemiology of 0157 in cattle. Nevertheless, there are still gaps in our knowledge. For instance, factors which explain why some herds do not contain 0157 await discovery. Risk factors that explain seasonal patters in 0157 prevalence are still being investigated. Also, the role of feed and water contamination needs further study to be clarified.

Because risk factors will typically affect either the herd or the within-herd prevalence of 0157, their influence can be modeled by adjusting the prevalence variables in this model relative to the baseline distributions after we account for the frequency of the risk factor among the population of herds or cattle.

There is a substantial amount of evidence concerning the occurrence of 0157 in live cattle. In this model our challenge was to coalesce this data into estimates of herd and within-herd prevalence. As it's developed, the model allows separation of variability from uncertainty. Such a treatment is a significant improvement. As the variability and uncertainty in this model's outputs are propagated through the other segments of the risk assessment, we will be capable of evaluating the importance of the production segment and the occurrence of human illnesses within the context of this uncertainty.

This is the end of my presentation. I'll be glad to answer questions.

MS. OLIVER: Does the Committee have any questions or comments, and all the experts too?

DR. HANCOCK: This is Dale Hancock, Washington State University.

I wanted to ask a question about the herd prevalence, particularly looking at the feedlot level. Just on theoretical grounds, if the feedlot prevalence were--in this estimate--80 something percent, as I recall, how would there--since feedlots get cattle from a large number of sources and feed, a number of loads of feed, that would be the two logical primary ways of getting E. coli-0157 into a feedlot, how would there be negative feedlots? Couldn't we assume that the feedlot-herd prevalence is 100 percent, on theoretical grounds?

DR. EBEL: I think that's reasonable as an

assumption. Empirically, that's more difficult to argue, but theoretically that would be a reasonable argument or hypothesis.

DR. HANCOCK: This is again Dale Hancock, Washington State University.

Maybe the heterogeneity within feedlots that wasn't modeled--and maybe it was, but you tell me--in the cattle on feed study, the largest study that you reported that had a 63 percent within-herd prevalence--or 63 percent feedlot prevalence, excuse me--those cattle were clustered. Those samples were clustered, because there were four pens in each feedlot with 30 samples per pen, and at least the empirical distribution in that stud of within-pen prevalence was strongly skewed to the right, suggesting a big-pen effect.

Could that account for the empirical estimate from your models of the feedlot prevalence? I mean, was that adequately modeled?

DR. EBEL: Well, I actually think it probably was because we are looking at--we handled herds the same way--I should say all the feedlots the same way, the distribution of the sampling. Our determinant in estimating herd prevalence is what was the apparent within-herd prevalence, and of course, that's a sort of weighted estimate based on using the results of both those pens that were shortest on feed, the two that had a random draw from sort of the middle, and then another sample from those that were on the longest feed. So that if there's a bias in there it would be in our inability to say that the estimate of within-herd prevalence or apparent within-herd prevalence from those feedlots is not weighted correctly, and to some degree, that might be in the data because of the higher within-herd prevalence in those pens that were shortest on feed. But again, they represented one of the pens, and then we had two that represented random draws, and then another from the largest, so possibly--I should say the longest--so possibly the longest and shortest had some canceling effect in terms of our estimate of apparent within-herd prevalence, but to some extent that might be true.

We did not explicitly try to account for that clustering because our argument was or our assumption was that across the four pens that were sampled on each herd, we probably had a good estimate of apparent prevalence across the entire feedlot.

DR. HANCOCK: This is Dale Hancock again.

To me, that's a decision that needs to be made, is whether or not this very high--all the studies there estimated very high feedlot prevalence, a very high percent of feedlots had it, and to me, it is justifiable to assume that the feedlot prevalence is 100 percent, but that's just something to think about.

Before I quit her, I wanted to ask a question also about the breeding herd prevalence, or the percent of breeding herds that had it. There's an extreme heterogeneity there, and I just want to make sure that we're modeling that adequately. Just to give you a sense of that, in that year-long study, '94, using relatively insensitive methods, admittedly, over half of all of the positives detected in that year-long study where they were sampled monthly were detected on the single sampling date with the most positives, and over 80 percent in the two sampling

dates, out of the roughly 12 per herd, with the most positives, and generally in the warm months of the year.

And so it's extremely temporally clustered in these herds, and in fact, over two-thirds of the sampling dates in positive herds were associated to no positive samples, herds that were eventually positive. Presumably it was missed, or in the environment or not in cattle there.

So is there adequate modeling for this very extreme level of temporal heterogeneity within these positive herds?

DR. EBEL: Well, as we pointed out in the scope presentation, at this point we are not incorporating seasonality into the model, and our rationale is that although there is some evidence in the live cattle research concerning a seasonal pattern, we don't have the corresponding evidence right now at the detail to sort of link it up and evaluate its importance in the subsequent segments: slaughter, preparation. So that's our justification at this point. It's basically a simplifying assumption.

To that extent then, the results from, say, a year-long study, of course, represent our apparent look at what the prevalence in those herds might be. Having made the adjustment we have for sensitivity, we feel like we've got a good picture, at least of average within-herd prevalence on a seasonally average basis, but I think we would all like to incorporate and feel like it is very feasible to incorporate seasonality into the model. Our precaution at this point has been basically that we don't have data downstream of live cattle to really establish that there in fact is a correlation, and as you will see as we model into slaughter, we have sort of a proportionality constant between live--incoming live prevalence and carcass prevalence. And that if that's constant and isn't adjusted for any sort of seasonal issues, it clearly is going to push through a seasonal pattern into ground beef contamination which may or may not be something we can empirically demonstrate.

So until we get that data, that's been our reason for being cautious and operating on sort of a seasonally-average basis.

MS. OLIVER: Dane?

DR. HANCOCK: And can I make one final comment?

And this is for the record. I think what you've shown here is accurate on the breeding-herd prevalence versus feedlot prevalence, and your reasons for that, in my view, are accurate, the age difference between those animals. But it's important, I think, to make, for the record, that those--it would be inaccurate to automatically assume from that prevalence data the feedlots had to two to three-fold higher prevalence, as I recall in your estimates, that something about feedlot management is causing that higher prevalence. Obviously, that's a good hypothesis that needs to be looked at, but it has been looked at to a certain degree, and there are several levels at which you can look at it, but within a dairy herd, for example, we have all age animals, and the--although the overall within-herd prevalence is low because we have mostly older animals, the prevalence within young stock within those herds is very similar to prevalence within feedlots. And when we have looked at dairy heifers in a dry-lot setting, because many

of the western dairies basically raise them in a feedlot setting, their dairy heifers, compared to those that put them on pasture, the prevalences are extremely similar. And so we need to make certain that we don't infer that that two to three-fold higher prevalence in feedlots is an effect of feedlots rather than age, because it's very similar to the age differences within dairy herds.

MS. OLIVER: Thank you. Dane.

DR. BERNARD: Thanks. Dane Bernard.

I'm glad Dale asked all those questions because those were confusing to me as well, but I'm sure I'm the only one in the group that is not a modeler, but in your summary comments you mentioned that variability uncertainty would be propagated throughout the model.

For my benefit, can you enlarge on what that means and what its effect is?

DR. EBEL: Okay, thanks. What we've tried to do, because this whole issue of variability and uncertainty is a real large issue within the risk assessment community, but isn't necessarily a similarly important issue for those outside, is to try to find a compromise that we think works for us, but basically we're taking and running throughout the model three scenarios.

The first scenario is the most likely scenario, and it's based on our best estimates of elements of--I should say--yes, variability in the various segments of the model. So the output we showed here for the most likely scenario represents the output based on our best estimates of what the average within-herd prevalence is, what we think the best estimate is with regard to herd prevalence in the corresponding parameters for feedlots. And we generate that output at distribution, which, as we showed, is the number of infected animals in say a group of 40, and that's the output that then goes into slaughter for the most likely scenario.

Then correspondingly we run two other scenarios which we'll also put into slaughter. One is the lower-bound and the other is the upper-bound, and they correspondingly have higher estimated numbers of infected cattle in 40-head or lower, depending on the bounds.

From the production, we are going to take those lower bounds and put them into corresponding lower-bounds for slaughter and upper-bounds, so that we'll end up having three scenarios that sort of trail out and demonstrate increasing uncertainty as we move progressively through the model.

At the end we'll describe the upper and lower bounds probabilistically of what we might expect based on our uncertainty in those inputs. And, again, that's the intent of it.

DR. BERNARD: Dane Bernard, again. In layman's terms, the greater the uncertainty at the beginning of the model, that's going to affect the next analysis and the uncertainty there as factored into the total uncertainty at that point and right on through the model.

DR. EBEL: Right.

DR. BERNARD: Thank you.

DR. EBEL: It appears to increase as we go along.

MS. OLIVER: Mike Doyle?

DR. DOYLE: Thank you. This is Mike Doyle, University of Georgia.

Eric, are we going to see any more about production data?

DR. EBEL: Today, probably not.

DR. DOYLE: Okay. Well, back to my original question. You came up with 11 percent shedding, and I haven't seen any numbers that come up to 11 percent in this presentation. So how do we get to 11 percent and a 102 to 103 per gram number of E coli being shed?

DR. EBEL: Okay. Well, again, as we pointed out, the 102 or 103 was just actually taken from sort of an expected value from I think the work you had done in calves long ago. But it was just a place holder. We aren't actually modeling contamination load per gram out of these cattle. We're primarily interested in what's the prevalence of cattle shedding.

But to get back to your first question about 11 percent, let's go to Slide 26 to show you the data that's driving up estimates for feedlot cattle.

Anyway, the Smith data is certainly in excess of 11 percent. It turns out that as we combine this evidence, make the adjustments for sensitivity, as you see the column there listing average apparent prevalence, those would be without making any adjustments for sensitivity of the test. So those are all going to go up in addition to the Smith data. As we go through the algorithm that we are obviously just briefly touching on, that's the data that generates an 11 percent average within-herd prevalence.

Because we are modeling within-herd prevalence is an exponentially distributed variable, however, that 11 percent is actually greater than what the median or the 50th percentile of that distribution would be, because an exponential is going to have a higher frequency at the lower within-herd prevalence levels. That's just a function of that distribution.

So I caution you to assume that that's the 50 percent break point, that 50 percent are greater than 11 percent and 50 percent or less than. It's actually 50 percent are going to be greater than some number less than 11 percent.

DR. DOYLE: Have you included the data that have been reported in the press recently from USDA which has these very high levels of carriage of 0157 by cattle?

DR. EBEL: Well, yes, I think we have to some extent, although we're never quite sure what, you know, is being referenced to what. But the Smith data is some very recent data, and it is part of the information that's coming out that's demonstrating much higher than previously report prevalences.

Also, the Lagreid study out of ARS is a recently published study, and their work continues. As they complete things, we try to get that information. But as yet, some of the information is not yet incorporated.

DR. DOYLE: Thank you.

DR. EBEL: Thanks.

MS. OLIVER: I'll take one more question now, and that'll be from Mel Eklund, and then after that go to the next presentation. If there's still more questions after than and the Committee wants to during discussion, you can ask them then.

DR. EKLUND: This is Mel Eklund from Seattle, Washington.

Most of the questions I had have already been answered by Dr. Hancock, but I have one other one that I would like to ask. Since Dr. Hancock is here, maybe he could answer it.

Have studies been done on cattle from rangelands, like in Montana, where it takes--I grew up on a cattle ranch there, and it takes 10 acres to raise one cow, and you have a very widespread--and most of these animals in these areas are--the breeding stock stays there, except sometimes bulls are brought in, so you don't have a lot of influx of other animals from these--have studies been done in these areas? And there are feedlots that come from--in the Montana area that come from these herds. I was just kind of curious what the incidence might be in this type of environment.

DR. EBEL: Yes, as a matter of fact, the Lagreid study, which, again, was recently reported--and I wanted to flip to that to see if I can--there were 15 cow/calf herds. Those were primarily range-type cow/calf herds were studied. They didn't do any sampling of cows, fecal sampling of cows in that study, so the data weren't appropriate for us to bring into the within-herd prevalence estimate, but they do show a fairly high prevalence of 13 out of the 15 herds that they sampled--and, again, that was across five Midwestern States, I believe--were found to contain at least one 0157 infected animal. But they sampled at weaning calves and that's the basis of their sample in that study.

DR. EKLUND: This is Mel Eklund again. Sometimes you get into the Midwest areas, these are smaller acreages. Some of the farms in Montana, you can drive 18 square miles on them. I was just kind of curious what the incidence might be in this environment.

DR. EBEL: When I say Midwestern, I mean--I grew up in Illinois, and I call that Midwestern. But I guess I'm thinking west of there. But they didn't--

DR. EKLUND: But that's small farms compared to Montana.

DR. EBEL: Right, right. And yet the ones that Lagreid worked in, they were in the Nebraska, Kansas type area. But I don't know that they incorporated any Montana herds in that study. Do you?

DR. HANCOCK: This is Dale Hancock. I don't know about that. We've really only done one study where we looked at cattle on range, and that was our earliest study where our methods were the most primitive. But we did find a really quite similar prevalence in range herds as in cattle herds, and we reported on one instance actually in West Texas where--and that's certainly an extensive type system--where cattle and deer shared common sub-types of E. coli 0157. And there's some recent work from Kansas, I believe, on surface water transmission, and certainly we're working on water trough transmission. And so there are opportunities for transmission in that setting, it appears, but there is a need for more data in the range setting.

MS. OLIVER: Thank you.

Our next presenter is Dr. Tanya Roberts, and she will talk on the issues of slaughter, and Karen Hulebak will discuss the questions that FSIS wants you to take into consideration.

DR. HULEBAK: All right. When you listen, as you listen to Dr. Roberts, please keep in your mind the following questions:

What evidence would be necessary to satisfactorily link, quantify the link between hide and carcass contamination?

And, second, we have attempted to develop a mechanistic model that follows product through the slaughter plant. Would it be preferable to develop a strictly data-anchored model that does not attempt to model processes between monitoring points? If so, what data would be required to develop such a model?

Excuse me. We're also going to try to help you track along in your handouts with the overheads that we use in these presentations. It's clear they don't track exactly point to point, but we'll give you some guidance on where to find a handout that more or less matches the projected figure.

DR. ROBERTS: Actually, I have a few extras. A lot of them have to do with some of the results we were able to put in at the last minute.

It's a pleasure to be here to talk about the slaughter segment of the E. coli 0157:H7 model. This slide identifies who my other collaborators have been on the team over the year and a half we've been working on it: Clare Narrad, Scott Malcolm, Jennifer Kuzma, Bob Brewer, and Peter Cowen. And we've also had comments from the other members of the E. coli team that were working on other segments of the model.

The outline is that I will discuss first the overview of the model structure, that we're looking at what kind of processes actually occur in slaughter plants. Second, we'll go into a description of the kinds of pathways that occur in the slaughter plant for 0157 contamination.

I'm going to discuss the event tree model assumptions and the data that we used, and let me just take a brief aside here that we tried to use in-plant data wherever possible and not the laboratory studies, because we were concerned that they wouldn't reflect actual operating conditions. Whenever possible, we used national data, but we did use some international data. We preferred E. coli 0157:H7 data rather than generic E. coli. And then, last, I'm going to give you some final conclusions about the model results and what the output is then to the next segment, preparation.

In the slaughterhouse, as most of you know--but not all of you work for the meat industry--live cattle enter the slaughter plant from the farm. They go to the knock box where they're stunned and bled, and they're hung on an overhead rail. They go to the next part of the main floor of the plant where the hide is removed, both mechanically and manually. Then they go through the first decontamination procedure to remove large fecal spots that are on the carcass, and sometimes they have a carcass wash.

Evisceration is the next step in the procedure where the gastrointestinal tract is removed. The next step is the carcass is split with a large chain saw. You'll notice that both this box and the knock box and stunning are not color-coded. That's because we did not include them in the model because the limited data that are available in the literature show that they were relatively low risk. That's something that we would welcome further data from, and we would be happy to add them.

The next step in the process is the second

decontamination procedure. This is after the carcasses are coming off the line and ready to go into the chiller, and in the U.S., two processes are used. Mostly the larger plants use a steam pasteurizer, and the smaller plants tend to use various kinds of hot water carcass washes, with or without the addition of various compounds.

Then the carcass goes into the chiller for one to two days. It's taken out to the fabrication room where it's cut up into steaks and roasts and chops, and the trim is put into a combo bin or boxes, which then becomes the output to the preparation segment.

You don't have this--no, I want to talk about this. You don't have this slide in your handout, but I thought maybe it would be useful to give you a little bit of an overview of the kind of a structure that we used in the slaughterhouse. We're using an event tree model, and we're building it for each step in the slaughter process I showed you on the previous slide. And we're looking at--each step we ask: Can contamination occur during this procedure? And this is a yes or no. If it can occur, then what are the possible levels of possible contamination?

For each one of these events where you have contamination and the levels of contamination, we ask what's the probability that this will occur, and we use a probability distribution to capture the variability and uncertainty associated with that.

Then, finally, we use a Monte Carlo simulation to take a random draw for each event in the tree, and we do 5,000 to 10,000 simulations depending on when you start to get stable results.

So what we want to end up with is being able to identify what the risk level is associated with different pathways that we are developing in our event tree model, and I'll discuss some of those pathways toward the end.

Next slide?

You also don't have this slide, but the point of this slide is to give you sort of an overview of the kinds of things that can go wrong in the slaughter process. These are the things that we're trying to capture in our event tree.

You could have a procedural failure, just a flawed plan for a process. There is some new evidence that hasn't been taken into account in an old operating procedure or just an oversight. There could be an operator failure, and those generally are of two kinds. One is the error of commission, you do the wrong thing. You don't clean your knife when you slit open the hide. Or it could be an error of omission, you just forgot to do something. You overlooked maybe one piece of equipment that you were cleaning the night before in the sanitation procedure.

You could have equipment failure. An example of this could be you could have a compressor that might fail in the chiller, and normally you have a back-up, but maybe the back-up failed. There could be a possibility here of equipment failure. Or, as you heard in the previous talk, you could have contaminated incoming product.

You do have this slide in your handout. For each step in the slaughter plant, we model the process and the pathway that could contribute to the risk, the sources of data for the input, and then the model. So this is going to be the similar structure that we're going to be talking

about for each one of the segments as we go through it.

As cattle enter the slaughter plant, they're trucks in, and as you heard reports, there's a possibility that they could have gastrointestinal contamination. They could be a fecal shedder. So the model is broken into two segments. We have one for steers and heifers and one for breeding cattle, and the steers and heifers, the feeding cattle, are modeled as one to five truckloads of 40 animals that come from one feedlot, and they have similar GI tract status on that feedlot. The breeding cattle, cows and bulls, are modeled as independent animals with GI tract status that's randomly picked from a national distribution of the prevalence.

These are the slides that Eric showed you. This is the one for steers and heifers, and looking at a truckload of them, what's the probability that they'll be-- you know, how many fecal shedders are they likely to have in that truckload. And he had the most likely, the lower-bound, and upper-bound scenario. And this is the slide you've seen before for a truckload of cows and bulls.

This summarizes the data on the previous two slides, and it's the percent of cattle that are likely to be infected by cattle type: the breeding herd with a 4 percent most likely prevalence, and these are the upper and lower bounds, and steer/heifer, 13 percent most likely prevalence. We've got to get together on this, Eric, because I think you said 11 was the most likely. We need to make some minor adjustment in these numbers.

DR. HULEBAK: Tanya, excuse me. Is this in your slide?

DR. ROBERTS: No. I don't think so, at any rate. No. You do have this next one, though.

DR. POWELL: Mark Powell. This was an effort to go back, review, and summarize the production that was being outputted into the slaughter model.

DR. HULEBAK: So we don't have this slide.

DR. POWELL: It's already been shown in the previous segment.

DR. HULEBAK: To the extent you can make note of that, it would be helpful.

DR. ROBERTS: For each one? Okay.

This is the event tree for steers and heifers. You have this truckload of 40 steers and heifers coming into the slaughter plant, and they could either come from a contaminated herd, so they have a possibility of the animals on that truck being contaminated, and so you would get to the individual animal basis so it has some probability of going--of staying--of being contaminated and going up this part of the event tree, or if the particular animal that's being slaughtered isn't contaminated, it will continue down this track. If the truck comes from an uncontaminated herd, then no animals on the truck will be contaminated, and it continues down this part of the event tree.

Once the animal is in the slaughter plant, then, the first part that we include in the model is the dehidng, and this is where the animal who has already been stunned and bled and is now dead enters the main part of the plant. It's upside down hanging from an overhead rail. Its hocks, or feet, are removed. The bung, or rear end, is tied off. The hide is cut down the midline, and the hide is pulled off manually and mechanically with a variety of side pullers, up

pullers, and down pullers.

The pathway that could allow contamination can occur via contact as the hide is removed with the contaminated hide itself slapping back on the carcass, with the worker's gloves or knives contaminating the carcass, or you could have aerosol contamination that could be created, especially if the hide puller moves rapidly and jerks the animal around.

You have this slide, but it's been changed a little bit. In the model part of the dehiding, we're going to be looking at three things. One is the area that's contaminated, the level of contamination, and on the next slide, we'll be talking about the probability of contamination.

The most likely scenario is that there are 3,000 cm² of the carcass that can be contaminated during the dehiding process, and this was the distribution--then we used a distribution to characterize our uncertainty about the exact size, and we have upper-bound and lower-bound scenarios.

The level of contamination is 1 to 3 logs of colony-forming units per carcass, and a Poisson distribution was used to characterize the uncertainty.

The data that this is based on comes from the combination of the FSIS carcass monitoring data that was discussed earlier and the FSIS ground beef sampling data.

Next slide, please?

The third component of this dehiding model is this probability of contamination, and here we relied on two English studies. The one that we relied on the most is Chapman--that was 1993--where they looked at a cattle slaughter plant in South Yorkshire, and they were looking, as I said, at cattle. But there was also an earlier study by Howe et al. which looked at a calf operation where they got similar contamination rates. Chapman was 30 percent; the Howe et al. was 33 percent. So we thought the Howe was sort of corroboration. And then we used this Chapman data, and they found seven carcass positives out of 23 fecal positives, so we put this into a beta distribution to capture our uncertainty about the exact number that would be contaminated.

The second part of the probability is to look at the possibility that subsequent carcasses following a fecally contaminated carcass could also be cross-contaminated. In the Chapman study, this was 8 percent. They found 25 fecal negatives that they tested that two of them actually turned out to have positive carcasses. Since they didn't contaminate themselves, they must have gotten the contamination from someplace else, from one of the other carcasses.

We used a geometric progression to capture this, and the first animal then that follows a fecally contaminated animal has a little over a 7 percent and the second animal has a little less than 1 percent probability of being contaminated.

Yes, you have this slide. So these are the event trees. You have a GI-positive animal coming in. You have, on average, a 30 percent chance that it will self-contaminate itself and a 70 percent chance that it will not contaminate its carcass as the hide is removed.

If you have a GI-negative animal that comes in,

we're looking at--if it does not follow a positive animal, it stays negative, it has a negative carcass. If it follows a positive animal, as I mentioned, we have--the next two adjacent ones have some probability of becoming cross-contaminated, but most of them will not be cross-contaminated.

The next step in the slaughter model is the first decontamination where we have knife trimming or spot steam vacuuming that remove visible fecal contamination. Sometimes this is also followed by a carcass rinse.

The pathway is that you can have removal of 0157:H7 if these procedures are effective, or you can just redistribute it over the carcass. If the knife is not cleaned in between cuts, it can transfer it from one location on the animal to another. Or the water rinse coming over can actually just move it physically down the carcass rather than actually get it all the way off the carcass. So we have both possibilities.

The model is based on data from two studies, Gill and Dorsa. Gill found a 0.32-log reduction, the Dorsa study found a 0.7-log reduction as their most likely values. So what we did was we built a trapezoidal distribution around this with a reduction of 0 to 1 log as being the whole range.

Again, there are only a few studies that were done, and it would be useful if we had more data here.

This shows you what the tree looks like. We have this contaminated carcass that comes along, and it has a possibility from a 0- to 1-log reduction with 0.3 and 0.7 being the most likely points here.

During a carcass evisceration, which is the next step that's modeled in the slaughter plant model, the process is that the GI tract and the rest of the organs are removed. The possible pathway for contamination is that you can have a rupture. You could have a knife nick, or there could be some weakness in the GI tract because of maybe some kind of an infection and it could rupture and come apart.

Now, it doesn't appear as though E. coli 0157:H7 is particularly likely to cause this. It's other organisms that could cause this kind of a rupture, so whether the animal's contaminated with 0157 is not likely to contribute to the probability of a rupture.

The basis of our model actually comes from Bob Brewer, one of our team members, who has extensive service in FSIS in investigating slaughterhouses, and he suggested that this self-contamination, this nick, could occur maybe one in 100 times. The contamination level is assumed to be equivalent to what we had in the dehiding earlier, and the area contaminated is smaller. It just ranges from 1 to 100 cm² with 25 cm being the most likely value.

So here you have this possibility of a positive animal either rupturing or not rupturing. If the animal didn't have any GI--any 0157 in its GI tract, it's going to continue negative. Even if it had a rupture, it would not cause contamination.

Next slide, please?

The next step in the model is to look at the second decontamination procedure, and as I mentioned earlier--oh, I see. We have carcass splitting in here, don't we, in you guys' handouts? Well, we didn't model

that, so I left it out of these slides.

So moving on to Slide 16 in your handout, the Carcass Decontamination II, the process here is that decontamination methods are used to remove or kill 0157 from the carcass exterior. At this point you have sides of beef because it's already been sawed in half, and the two most common techniques used by U.S. industry are steam pasteurizer, in which these railed carcasses enter the steam pasteurizer four at a time. This stainless steel clamshell shuts around them. The air is blown in to blow the water off the exterior of the carcass so that the steam can penetrate, and steam of 180 to 210 degrees Fahrenheit is applied for 5 to 15 seconds.

Most small and medium plants use a hot water wash, although there are a few large plants that also use the hot water wash instead of steam pasteurization. And here you're using the heat as well as the volume of the water coming over the carcass as methods of either dislodging or killing the 0157. You also have the possible addition of organic acids or trisodium phosphate. And the efficacy is going to depend on the heat and the volume of water used.

The pathway is that you can have--where you can have a change in the risk status is that the carcass wash is going to either reduce or redistribute the organisms, and the steam pasteurization can significantly reduce contamination. However, low temperature use is not effective.

The data that we actually put into the model for steam pasteurization, we used a triangular distribution with a range of 0 to 2 logs--this is based on Gill's work--and with 1-log reduction the most likely.

For the hot water wash, what we did was we modeled this the same way, that trapezoidal distribution, as we did in the first decontamination procedure.

This shows the event tree pathways, then, for the second decontamination. This shows the steam pasteurizer. You have from a 0- to 2-log reduction with 1 log being the most likely. And so you take a random draw from this if it went through the pasteurizer to see what level of reduction you actually got for the particular Monte Carlo simulation. And, again, if it's an uncontaminated carcass, it goes through this decontamination procedure, it's going to remain uncontaminated.

The next step in the model is carcass chilling, and the process here is that you have--sides of beef are blast air chilled for 18 to 48 hours. The pathway is that you can get growth or decline of E. coli 0157:H7 on the carcass surface, and that's going to be a function of both the time and the temperature. And you can also have cross-contamination from other carcasses, and that's going to be more likely the more crowded the chiller is.

In the model, we pooled data from three slaughter plant studies, from Dorsa and from Gill and Bryant, to come up with a common distribution, with a normal distribution, where the mean is 0 and a standard deviation of 1.

This is the event tree. You can hardly see these things. What we did was we assumed--and this is something that we're thinking of perhaps changing. We have this contaminated carcass that comes in, and we're assuming that the truckload is all going to either go into a chill--well, it will go into the same chiller. But in that same chiller,

you'll either get growth or you'll get decline. It depends on the efficacy of the chiller.

I was recently in New Zealand, and there they were suggesting that there is so much variability; even on the carcass you can get 5 degrees Centigrade difference in the air coming onto the chiller and the air going--let me stop. Air that comes on--the temperature of the air coming onto the carcass and the temperature of the air going off the carcass, there can be a 5 degree Centigrade difference.

So I had been thinking about this as being-- looking at physically the chiller and how it's located and how close the carcass is to the door that opens and closes, or how close it is to the blast air chiller coming out, it would be cooler there, or how crowded it is. So I was thinking of a fixed room with sort of the geographical flow of air in that room.

But they were also suggesting, too, that you need to look at the differences in temperature even on one carcass, which was a whole new concept, and they have some data that they're willing to share with us, so we might try to complicate this part of the model.

But, again, if you have an uncontaminated carcass, we're not really modeling the cross-contamination that possibly could occur. We're assuming it stays negative.

What this tree does--and you do have one of these in your slides. It doesn't have--

DR. POWELL: This is Slide 28 in your handout.

DR. ROBERTS: Oh, it's in a different location.

I'll be coming back to talk about fabrication later.

What this event tree does here--and it's labeled slaughter event tree in black, so it's a little hard to read up here--is it summarizes all the steps in the slaughter process we've discussed so far. So we have the incoming fecal status of the animal. What happens is the hide is taken off, what is the carcass status, what happens during the decontamination, evisceration, second decontamination, and the chiller. And at the end over here, you're coming up with, for each pathway in the event tree--so here's one pathway, and, you know, here's another one. You have these 19 pathways, and each pathway in the event tree has a probability and a level of carcass contamination associated with that pathway. Then you want to know how many pounds of meat actually end up going on these different pathways.

These boxes in black here indicate negative pathways, so you don't have to be worried about those. Fortunately, most of them are negative. However, there are five positive pathways, and I thought I'd give you a little bit of discussion on each one.

Starting at the top, S1 ends up with a positive carcass. You have some contamination here. And that's because you had a positive animal come in and it contaminated its carcass. It's F-positive and C-positive. And then, in fact, it even went on to contaminate itself during evisceration, too. So that's not going to be a very likely event because evisceration is a low probability event, only 1 in 100 times does that happen, you get any contamination there.

The next pathway, S4, is a little more common, and that's this one right here. You have a positive animal coming in. It contaminates its own carcass, and then it gets some reduction during contamination, but it's not zero.

So it ends up being contaminated.

S7, you have this carcass that comes in--I mean that's fecally positive, the carcass is positive, and it goes through decontamination so that it now becomes negative during the first decontamination procedure, but then it contaminates itself during evisceration.

S15 is where you have a negative carcass that comes in--I mean, a negative animal that comes in that gets contaminated by a preceding carcass, so it becomes C+ in the dehidig and that causes the contamination. And S15--oh, that was that one.

DR. HULEBAK: S11?

DR. ROBERTS: Yes, I guess I was talking about 11. No, wait a minute. No, that was right. Then S11, yes, is the one I've left out. Thank you. That's where you had a positive animal come in, it did not contaminate at carcass, but it got contaminated in evisceration. And that's also going to be a low probability pathway.

So the pathways that are most likely in this scenario are S14 and S15. They're going to be the most likely contributors to contamination.

DR. HULEBAK: S11 and S15?

DR. ROBERTS: S4 and S15. Yes, S4 and S15.

This slide you don't have in your handouts, and what it does is it summarizes the data in the model looking at the probability of a carcass being contaminated. And, again, it's broken down by cattle type. For the cow/bull herds, you have a 0.3 percent most likely prevalence, so only 0.3 percent of the carcasses will be contaminated. The upper bound is 2 percent and the lower bound is 0.14 percent.

For the steer/heifers, you have about a three-fold greater probability with the most likely prevalence for the carcass being contaminated 0.98 percent. So it's less than 1 percent. Upper bound 5 percent, lower bound 0.5 percent.

The next step in the process--

DR. POWELL: If I might, this is Slide 21 in your handouts.

DR. ROBERTS: Thank you, Mark.

DR. HULEBAK: Page 11.

DR. POWELL: Page 11, No. 21.

DR. ROBERTS: This is the last step in the slaughter model. In fabrication, you have the carcass coming in on a rail, and it's cut into steaks and roasts and other cuts, and the trim is put into vacuum package pieces, boxes--well, the trim is put into the boxes and the combo bins.

For your explanation--you may not know what these combo bins look like. They're these enormous cardboard boxes that are either round or hexagonal-shaped, and they're lined with an enormous plastic sack, which they then tie off on the top once it's full. It will hold 2,000 pounds of meat, more or less, and they put it on a forklift before they even load it, you know, when it's empty, and then--I mean, they put it on a wooden pallet that a forklift can then lift up and put it right onto the truck. And you end up then with--some of these trucks, you know, have up to 20 combo bins that will be on them, and then they'll take them off to the grinder from the slaughter plant.

Or if they don't have an immediate shipment going out, it may be put into the chiller, or they may actually

grind some on a plant and it'll go into a room, be refrigerated, waiting until they grind it on the premises. So you have this product coming in from the chiller, and it's cut into trim and put into these boxes or combo bins, and some of the product is sent off site, et cetera.

There was a question earlier about the ratios that we used, and here in this fabrication process for a steer/heifer plant, you have--trim from one steer/heifer may go into five combos, or there may be 30 to 100 animals per combo bin. You'll see on the next slide or the one a couple slides later that 18 percent on average of the meat from a steer/heifer ends up as trim, and the other 82 percent goes into roasts and steaks and chops.

For a cow/bull plant, typically the trim from one animal goes into two combo bins, but there may be up to 20 animals per combo. And it depends partly on what kind of lines they have set up, what it is they're trying to take off the animals, as to how many they have. And from a typical cow, on average you have--54 percent of the product does end up into the combo bin. These are older, tougher animals, but they do increasingly, with the improvements in tenderization, take off more of the roasts and other cuts to use in other products, whereas almost all of the bull meat ends up in the combo bin because it is even though and I guess has a stronger flavor as well.

The pathway where you can have potential contamination is you can have detritus stuck on to the equipment, and earlier contaminated meat can contaminate the fabrication line, which, you know, then that contamination can then be transferred onto subsequent pieces of meat that come down that conveyor belt, or contaminate the knives or whatever else

You can also have growth of E. coli 0157 if the fabrication room temperature is not controlled. Typically, it's at 50 degrees or less.

Next slide?

The level and probability of contamination during fabrication is dependent on--

DR. POWELL: This is Slide 25, page 13 of your handout.

DR. ROBERTS: --is a function of the plant level quality, and Scott Malcolm on our team developed this index. And on the x axis you have the level of contamination CFUs per cm². On the y axis you have the probability of contamination.

For a plant of good quality, you're going to have low levels of contamination, and it's going to be under strict control. You're going to have a very narrow variance. For plants that have not as good control over the quality, you're going to have higher levels of contamination on average for the pieces that come through there, and you're going to have a greater variability associated with that. So that's the kind of distribution you get.

In the model we have roughly 50 percent of the plants have no change in contamination, no increase, one-third have a 1-log increase, and 16 percent have a 2-log increase.

Next slide?

So in the fabrication model, then, you have the probability and level of contamination that is going to vary from plant to plant, depending on the plant quality. You

also going to have a probability and level of contamination that will vary by cattle type. As you've seen earlier slides, we talked about the differences in the prevalence of contamination depending on the incoming cattle, depending on what type they were, steers and heifers versus cows and bulls.

You also get a more minor effect due to the differences in the carcass surface contamination in the combo bins that varies by the cattle type, and this is shown on the next slide, which is your Slide 26. It's slightly different. We have an extra column added on here. And what this column does is this shows you the difference in carcass weight depending on the animals. You know, the male animals are slightly larger. And the percent of meat we're assuming that the hide--I mean that once you have a carcass and you take out the bone, the 70 percent that's left is your meat, that 30 percent of it is bone, that the percent of the carcass that's going to end up in the combo bin is going to vary, as I mentioned before, so steers and heifers, it's 18 percent; cows, it's 54 percent.

But you also have this difference in the percent of the contamination that's on the surface of the carcass that's going to actually end up in the trim, and we're thankful for Todd McAlewn (ph) for giving us the information for the steers and heifers which we extrapolated to cows and bulls.

What this means, then, is that when you look at the ratio of the contamination to the trim percentage, you get very different ratios, with the steers and heifers actually having a higher probability of having any contamination that was on the carcass actually ending up in the trim than you do for the cows and bulls, which have a different ratio because they have more sterile meat from the interior of the carcass versus the exterior.

Next slide?

These next two slides you don't have, and it's the summary of the data of the model so far, and what I want to emphasize here is that the "nc" means not contaminated. This shows you for the cows and bulls the number of combo bins that are not contaminated, and if they are contaminated, what the log contamination ratio is. So for the most likely scenario, which is in the middle here, 95 percent of the combo bins will not be contaminated. The upper and lower bounds are 98 percent and 77 percent. And then you can see that you're getting very low levels of contamination in this 2,000-pound combo bin.

Next slide, please?

The steers and heifers are slightly more contaminated because they're coming in with more contaminated animals and you have this ratio of this trim, the exterior-to-interior effect that I showed you two slides ago. The most likely scenario is that 72 percent of the carcasses--of the combo bins, excuse me, for steers and heifers will not be contaminated, with the upper and lower bounds of 83 percent and 34 percent.

You can see that the log levels is also slightly greater for steers and heifers than it is for cows and bulls, but it's still at very low levels.

This is a summary of the data on the previous two slides, and, again, you do not have this, but we'll send it to you. This shows you the most likely prevalence of E.

coli 0157 levels in the contaminated combo bins. So we've taken out the uncontaminated ones, and we're just looking-- no, wait a minute.

I don't know if this is levels or percentages. Eric, does this make--what is this?

DR. EBEL: Those are the prevalences of the contaminated combo bins on this slide.

DR. ROBERTS: Okay. So this would be the average of the whole table shown on the previous slide, the contaminated and the uncontaminated?

DR. EBEL: The portion of all combos that are contaminated.

DR. ROBERTS: Okay. So it says then 4.8 percent of the cow/bull combo bins have some level of contamination, and 28.1 percent of the steer/heifer combo bins have some level of contamination, although it's low levels. And this shows you the upper and the lower bounds.

I forgot; it's these next three slides that show the levels. I was jumping ahead of myself here and getting confused.

So you've seen these slides before in Eric's part of the talk where we're looking at the distribution and with the most likely and upper and lower bounds of contamination. This is the cow/bull scenario, and this one is the steer/heifer scenario for the uncertainty about the 0157 levels in the combo bins.

This slide is a summary slide, what shows you the levels in those combo bins that are positive. This is the slide I thought I was looking at three slides ago. And by cattle type, you can see what the levels are on average in these contaminated--you have that whole distribution before, but in the cow/bull combo bin, you're only talking about 1.15-log CFUs per 2,000 pounds of meat. And in the steer/heifer, it's 1.44 CFUs, slightly higher, per the whole combo bin of 2,000 pounds of meat.

Just a couple of wrap-up comments about modeling variability and uncertainty. As Eric mentioned, variability is a state of the world, and in developing this model, I was really impressed with when you're trying to look at the impact of a whole industry, you're going to have quite a bit of variability in these models, and much more so than the models of individual plants because you have so many different kinds of processes. Different kinds of things can go wrong in plants with different procedures, and you're trying to capture all of these different events in your model.

Next slide?

The uncertainty in our model is a function of the limited data on plant processes, the limited data on the performance of these processes, and the problem of measuring cross-contamination. I'd also like to point out that we can reduce our uncertainty greatly by collecting better data on each one of those three points and by also improving our modeling of the physical process, and I talked about what we might be doing in the chiller as an example of this.

And I'd like to close then with this last slide, that some of the future modeling scenarios we're thinking of looking at would be to see what impact reducing the levels of incoming 0157 on the incoming cattle had on the impact of the probability and levels in the beef trim, and then also

to explore various kinds of changes, either the worst and the best practices in the plants and what these have on the impact on 0157 contamination. This would be during all steps that we've modeled: the dehiding, evisceration, decontamination, steam pasteurization, chilling, and fabrication practices.

And we did have some data that was submitted to the docket from Foodmaker, and they have a rather extensive program for testing, and we would like to see if this then-- if we went to some of our best practices and compared them with the Foodmaker combo bin data, what our results were.

Thank you for your attention, and I'm ready for questions.

MS. OLIVER: Does the Committee have any questions, and the invited experts? Art?

DR. LIANG: Art Liang, CDC. I'm going to probably get gasps from the audience. I'm going to ask a stupid question. The models by their very nature are simplifications over reality.

DR. ROBERTS: Yes.

DR. LIANG: So I was wondering if you or anyone on the team could discuss by what criteria you choose to simplify collapsed steps versus increase your precision in describing a given step in a model?

DR. ROBERTS: Well, so far what we've done is we've just looked at the literature and whether the data seems to indicate that it's a very risky step or not. Now, it could be that it's just not in the literature yet, that nobody's chosen to study that particular thing, whether there is a high-risk practice going on. So there could be some ignorance on our part here.

On my last slide, I talked about how we're going to be looking at changes in practice and how they affect the model. Well, they call that sometimes significance analysis or importance analysis, and that will show us how robust our model is to the various things that we've assumed, you know, we put into the model, and then we could possibly be making some adjustments at that stage if we find out that things that we thought were important aren't really important.

I don't know. Does any of the team members want to add some more comments to that?

MS. OLIVER: Dan?

DR. ENGELJOHN: On that issue?

MS. OLIVER: No.

DR. ENGELJOHN: Dan Engeljohn. Tanya, on the-- it's Slide 22 in our handout, but it's 29, I think, that was on the screen, going back to the issue of carcasses represented in a combo.

DR. ROBERTS: Yes.

DR. ENGELJOHN: In the comment period that we had out on 0157, we got information that the combo bin would represent 300 carcasses. So--

DR. ROBERTS: Would represent how many?

DR. ENGELJOHN: Three hundred.

DR. ROBERTS: For the steer/heifer plants?

DR. ENGELJOHN: I don't--we didn't get a distinction between steer/heifer or cow/bulls, but I'm just curious as to where you got your information, and that may be something we need to follow up on.

DR. ROBERTS: Yes, I actually thought that--on the team, Clare was actually handling the fabrication part, and

I thought that she had followed up on that and made any changes. So, frankly, I'm sorry, I can't say. But she had originally talked to several members of people in the industry in developing that part of the model.

But each plant is going to be a little bit different, too, in the way they operate and the size of the animal they get, the kind of breed that they get in. So, you know, I think--I don't know that it would be any fewer than 300, so maybe you're just saying we ought to raise the upper end of that range so it would be 30 to 300 rather than 30 to 100.

MS. OLIVER: Roberta?

DR. MORALES: Roberta Morales, Research Triangle Institute. Tanya, I was curious. When you were talking about fabrication and you were talking about how they were starting to fill these combo bins--

DR. ROBERTS: Right.

DR. MORALES: --that some of them were directly trucked out and others were stuck in the chiller. Are all of them kind of--I would assume--you said there was a fairly large number of them that went into the truck. Are they loaded--

DR. ROBERTS: Right, 20.

DR. MORALES: Twenty? Are they loaded directly onto the truck or--

DR. ROBERTS: Yes, with this forklift thing. They just--

DR. MORALES: Okay. Is that going to affect the temperature at which they're stored while they're waiting for the truck to be loaded versus if they were chilled? And is that going to affect growth?

DR. ROBERTS: Well, Wayne actually has that part in his model, but, you know, they actually keep these fabrication rooms at 50 degrees, and the trucks are backed up and they're opened to it so the temperature in the truck is also 50 degrees or less, too.

DR. MORALES: Okay.

DR. ROBERTS: If that's your question.

DR. MORALES: And so when they go into the combo bins, they're already pretty much at 50 degrees temperature.

DR. ROBERTS: Well, they've been chilled for 18 to 48 hours.

DR. MORALES: Okay. So they are pretty much--the other question I had--

DR. POWELL: Before we leave that point--this is Mark Powell--I think Wayne will respond also to that comment. We have dealt with growth primarily in the preparation segment.

DR. SCHLOSSER: I'll just cover that briefly. I'm Wayne Schlosser--

MS. OLIVER: Can you say your name?

DR. SCHLOSSER: Wayne Schlosser. We actually have a range of variability of storage practices that we handle before grinding and after grinding and then on through preparation.

DR. MORALES: Okay. I had one other question. When you were describing the incoming steer/heifer contamination, I don't know much about how cattle are transported, but in thinking about poultry, when you have a flock that's--you know, they may or may not be positive, but the cages in which they're transported can affect whether or

not they end up in the slaughterhouses positive or negative.

I was wondering, when you were looking at that, whether or not you considered separating out in your decision tree there looking at animals that are contaminated versus not contaminated, and then thinking about whether or not the transport--the truck was contaminated or not contaminated, because that would ultimately affect what your proportion of contaminated animals would be. And I was just thinking about this quickly, the way you have this model, you would have one in three scenarios in which the animal would be contaminated, whereas if you looked at animals first and then trucks as contaminated or not, you could potentially have three out of four scenarios in which they would come up contaminated, which would be a substantial difference.

DR. ROBERTS: Eric, would you like to answer that since you handled that in your part of the model? Nice to be able to do a hand-off.

MS. OLIVER: You need to speak into the microphone.

DR. EBEL: Eric Ebel again. I think the point you raise is a real good one, and that's why we've tried to emphasize the need for evaluation of high contamination because really we think that that environmental source of 0157 is going to relate more to hide than intestinal carriage. Again, the reason we're limiting our incoming depiction of 0157 in live cow right now to fecal shedding is that's what data we have to link it to the carcass. But it's clearly a more complex process than we're currently modeling, but that's where we're limited right now is that data linking live to carcass.

Thanks.

MR. SEWARD: Skip Seward, McDonald's Corporation.

Just a couple of questions, Tanya. On the carcass evisceration discussion that you had relative to the self-contamination. Are you referring there to like puncture of the intestinal tract?

DR. ROBERTS: Yes.

MR. SEWARD: And you mentioned that that occurred or you were given information that that occurred 1 in 100 times.

DR. ROBERTS: Right.

MR. SEWARD: And I'm just curious--it seems like there would be real good information on that from inspectors, because I think if that event occurs in a processing facility, that has to be documented. And I just don't--it seems like that's a much higher frequency than at least what I've been told actually occurs in a production facility, but I would think that that would be documented and very easily obtained from inspection reports in a facility.

So you said you got that from somebody who worked in your group and I don't know--

DR. ROBERTS: Yeah, Bob Brewer.

MR. SEWARD: Maybe that's where they got that, but that seems--

DR. ROBERTS: I'll ask him to double-check on that, because, frankly, I'm not familiar with it exactly.

MR. SEWARD: Thank you. The second question. In regard to steam pasteurization, on our slide 17, where it talks about you had a triangular distribution range of 0 to

2 logs.

DR. ROBERTS: Right.

MR. SEWARD: I guess what I'm curious about there is that does that suggest that you could run a carcass through a steam pasteurizer and have zero impact on the microbiological load?

DR. ROBERTS: Right.

MR. SEWARD: And, again, in talking to everyone I know in the industry who uses steam pasteurizers, all the big processors, I doubt if they would agree that if you run a carcass through a pasteurizer that there's a likelihood that--any likelihood at all that you would have no impact whatsoever on--

DR. ROBERTS: Well, it's a very low probability event, because on the triangle, that is just the final endpoint, and the most likely is that you'll get 1 log, and then you have up to 2 logs.

Now, maybe Colin Gill, since I've used your data, maybe you would like to discuss what you found in the plants.

DR. GILL: Well, I think the--Colin Gill.

If the steam pasteurizer is operated properly, then you'll get a 2-log reduction, but there's a tendency in plants to screw down the temperature and reduce the time so as to not affect the appearance of the carcass, and the literature suggests that at least some plants, these things are being operated at ineffective times and ineffective temperatures. So the zero effect is probably quite reasonable in some circumstances.

MR. SEWARD: Well, that's something that you might want to check out because all of the raw material suppliers I know that, having made that kind of investment, are not cheating on the operation of those pieces of equipment. So I would--if there's someone out there making that kind of investment, and then trying to cheat on the equipment, I've never heard of that, and I think before you just accept that as fact, you'd want to have some real good hard facts to support that.

DR. ROBERTS: Well, maybe McDonald's would like to share some information with us, submit it to the docket.

MR. SEWARD: I'll certainly talk to the people who are operating that equipment, and let them know that someone is indicating that, you know, that those are not being operated up to performance, because that's certainly not the experience that I've seen.

DR. GILL: Could I just mention that I'm not saying that I have knowledge myself--

MS. OLIVER: Can you identify yourself again, please?

DR. GILL: Sorry. Colin Gill--that I have knowledge of anybody who's not operating it. There's very little in the literature, but what is published in the literature, there is one case where the equipment apparently was not being operated as an appropriate--for an appropriate time and at its appropriate temperature, and in which they were recovering substantial numbers of E. coli from the treated product. So one can only assume that some cases this is happening, because this was apparently a commercial processor.

It would definitely be very well worthwhile finding out what was really going on with the use of this

sort of equipment, because I'm sure that some people apparently do not understand how it operates.

MR. SEWARD: A couple more questions if I may. One on carcass chilling. Wouldn't a third possibility be that there would be no change? You indicated that you would get--potentially you could get growth or a decline. Wouldn't a third possibility just simply no change, or maybe that's captured and I just missed it?

DR. ROBERTS: Yeah. Maybe I didn't point it out very well either. It's the slide that looks like this.

[Laughter.]

DR. ROBERTS: You can't see these distributions very well, but it actually is a normal distribution with the most likely value being zero. And we've had truncated into half so that you're either going to get growth--but, see most of it, the greatest percentage actually is at zero, or a decline.

MR. SEWARD: Yeah, sure, okay. That's my problem. Thanks.

On the level of contamination during fabrication, I think you mentioned that there were some decisions made on plant performance, a certain percentage were good, a certain percentage were bad, if you will, and a certain percentage were--

DR. ROBERTS: Right.

MR. SEWARD: Where did those numbers come from? If you can help me understand how--I didn't quite get the numbers because I didn't see them in here, but I was just curious how you arrived at--how the plant performance--

DR. ROBERTS: Well, we had three studies, but you know, it doesn't seem to be mentioned. The data doesn't seem to be mentioned on my slide, so that's an oversight. But Scott took--pulled the data from these three different studies, and put it together to build this plant quality index. We'll have to provide that to you.

MR. SEWARD: Thank you.

I just have one more question, and that is that if I interpret your model output baseline results correctly, does that suggest that the model indicates that if you're using steer heifer meat, that 28 percent of the time you're using meat that is adulterated, and that if you put that into ground beef, based on some earlier slides, that that's going to be multiplied or doubled at least, and so potentially something like over 50 percent of--according to the model--over 50 percent of the ground beef coming from steer heifer beef would be adulterated?

DR. ROBERTS: It says that there's 28 percent of the time you will have one organism or more in the combo bin, so when you think of on a per-patty basis, you're going to--if it's quarter-pound patties, you're going to have 8,000 patties, so you'll have--you know, if it's only one organism, 7999 will be uncontaminated. But the combo bin itself will have 1 organism or more.

So Wayne will talk a little bit more about how that replicates throughout the model.

MR. SEWARD: But for an answer to my question, I'm sort of--because on an adulteration basis it's on a lot basis, and it wouldn't matter whether you had one patty that potentially contained 0157:H7 or all of them.

DR. ROBERTS: If you're asking about the policy, I don't know how to answer it.

MR. SEWARD: No. I'm just trying to interpret the data. Is that what the data is saying, is that the prevalence is that if--at least in raw materials--that 28 percent of the time you're going to have adulterated materials or it's going to contain E. coli--don't use the word "adulterated"--it's going to contain 0157:H7.

DR. SCHLOSSER: Hi. This is Wayne Schlosser again. Yes.

MR. SEWARD: Okay, thank you.

[Laughter.]

MS. OLIVER: Dale?

DR. HANCOCK: I have a couple of comments.

MS. OLIVER: And can you identify yourself again?

DR. HANCOCK: Excuse me. Dale Hancock, Washington State University.

You're validating this to some extent with MPN counts from FSIS sampling; am I right? Well, I should probably start out saying I'm an epidemiologist who's been forced into some microbiology, so maybe I don't understand this totally, but to me that should be called an MPN index rather than an MPN count, because basically we make a dilution tube series, and it's the MPN count, only under the assumption that at that endpoint dilution we can detect those tubes with one and only one organism in them, and I would go on record as saying that I doubt that the 50 percent detection endpoint for a single tube is as low as 1 or even as low as 10. And so I think that number is probably at least ten-fold lower than reality. At least, that's--I think that should be considered, and maybe for people who know more microbiology than I do would comment on that.

I have one other point. Should I go ahead--

MS. OLIVER: I don't know if Eric and Wayne would like to say anything in response to Dale on that? Since Eric talked about the testing. Well, maybe Bill would like to comment on that too.

DR. EBEL: This is Eric Ebel. I guess our response is that we used the most probable number estimate as our most likely scenario, but we do have boundaries that are intended to be incorporated both the uncertainty and the MPN method, as well as just measurement error in the general sense. Again, we only have four observations on concentration estimates anyway. But your point is well taken. You know, the way we've tried to adjust for that is in our uncertainty about what we think the distribution looks like.

DR. HANCOCK: And it will relate at the retain or consumer level too, because when we hear--like in the 1993 outbreak, a certain number of CFU per gram, I'm not certain if that's adjusted for the analytical sensitivity of that MPN procedure, and it certainly should be, just from an epidemiologist's viewpoint, because almost certainly the measured MPN count is much lower, perhaps by 10-fold than the actual count.

The other point I wanted to make--I think Dr. Ebel--this is Bill Hancock by the way; I didn't say that. Dr. Ebel mentioned it, and I just wanted to reiterate. That is, the hide thing is probably more important than we're seeing. He cited a little piece of work we did that suggested 1.7 percent hide prevalence, but that was one little dung lock as the carcass was--or the animal was

swinging by, and almost certainly the whole--if you had some way of measuring the whole thing, it would be higher. And actually there's data in--somewhere in Meat Animal Research Center, not readily available, I guess, that indicates the hide prevalence is much, much higher than the 1.6 percent, and that is an area that I think we're going to have to focus on more.

MS. OLIVER: Colin?

DR. GILL: Yes, thank you. Colin Gill, Agriculture, Canada.

I'd just like to make a few comments on the presentation. You refer to UK data--data from a UK as to cross-contamination. I'd suggest you should handle that with extreme caution because that plant is unlikely to be anything like the high-speed plants in which most of the carcasses, beef carcasses are dressed in North America.

Trimming, steam, vacuuming, washing, my own conclusions were that none of these are effective at all for removing bacteria from carcasses, although they're useful for removing visible contamination.

One thing that sort of puzzles me about both this presentation and the previous one is that nobody considered contamination from the head of the animal. I know that there's a keen veterinary interest in the other end, but take any head removal, the head meats are heavily contaminated with generic E. coli. The head can be handled extensively during the--during its removal, and you would spread presumably 0157 would be--I'll go along with that.

I'd also be interested to know from the veterinary people present what would be the relationship between E. coli carried in the stomach and E. coli in the feces? Is there any necessary relationship between the numbers involved there? Could there be a situation where you've got some in the stomach and none in the feces and vice versa?

Modeling chillers, I wouldn't try it if I were you. The air flows in these things are perturbed greatly by the way the chillers are loaded, by the size of the carcasses, by all sorts of things, very, very difficult to get a detailed results. You can, however, get gross results, and it does appear that in almost any chiller a fraction of the carcasses will be improperly--will be inadequately cooled simply because the air flow has been perturbed and they're not being affected by it.

On the other hand you can see the gross effects of chillers quite easily, and some, particularly those which do not employ spray chilling, you do tend to get a substantial reduction in E. coli numbers, but it does not appear to be additive with treatments like steam pasteurizing or the steam pasteurizing treatment's affected the subsequent reduction due to a decontamination chilling process will be modest.

The main point I wanted to make was that some recent work we've been doing during the last year or two, has indicated that the majority of generic E. coli that are found on manufacturing meat, emerging from slaughtering plants, is deposited on the meat during the cutting processes. The sources of this contamination appears to be inadequately cleaned equipment used in the cutting process. This is not to say that people aren't trying to clean it; they just don't realize that there are areas in their equipment that they can't get at, that they can't see, and

when you get in them and have a look at them and dig the stuff out, you can find that this is carrying E. coli.

The increase in numbers can amount to average increases of more than 4 logs, so it appears that in talking about the bacteria on the carcass, you're talking about something that is a disappearingly small fraction of the total load that goes out on the manufacturing meat, and most of that is in fact coming from improperly cleaned carcass breaking equipment. And if you want to do something about the problem, that would be the place to start, because it appears not to be widely recognized, but this is happening. Thank you.

MS. OLIVER: Dane?

DR. BERNARD: Thanks. Dane Bernard.

I'm not sure I have anything to compare with what Dr. Gill just shared with us. However, Tanya, your outputs, Dr. Seward had called attention to the numbers in the baseline results, and even in your best case scenario we had 17.1 percent of combo bins with 1 or more 0157 in them. And then I glance down at foodmaker data and notice, obviously, a substantial difference. The obvious answer, I suppose, is because foodmakers is actually based on testing, and you're not going to test the whole combo, whereas yours predicts contamination in a combo of 1 cell. But is there anything else we can glean from that? The numbers are strikingly different.

DR. ROBERTS: We haven't really integrated the foodmaker data into our analysis yet, so I can't really comment fully on that.

MS. OLIVER: Mike?

DR. ROBACH: Mike Robach.

I just wanted a point of clarification just for my own mind. In your model assumptions, I just want to make sure I understood this, of the carcasses that enter a plant that are contaminated, are fecally contaminated, visibly contaminated, am I to understand that your model is assuming that 30 to 33 percent of these carcasses will be positive for 0157

DR. ROBERTS: No. It's saying of those that have 0157 and are shedding them as they enter the plant, and that of those that have--that are positive for 0157, that 30 percent of them will contaminate their carcass as their hide is removed. But the actual levels that have come from Eric's data on the incoming cattle or the numbers that are positive for 0157, is that your question?

DR. ROBACH: Well, I guess I'm a little confused, because I thought when Eric--this is Mike Robach again--when Eric was concluding his presentation, I thought he said that visible soiling was not a good predictor of carcass status.

DR. ROBERTS: Right, it's not. So these are actual--these are estimates in his model that coming into the slaughterhouse, of what percent of those animals actually have 0157 in their gastrointestinal tract and are shedding the organism. That's the number we're using. We're not using whether they look fecally contaminated or not.

DR. ROBACH: I also thought that he said there was no correlation between fecal and hide status. I'm just a little confused, you know, how this is all flowing. Maybe Eric could enlighten me.

DR. EBEL: This is Eric Ebel.

The critical, I guess, term in those things is "visible", and our study that we were referencing there basically just used gross indicators of degrees of dirtiness, if you will, of the hide. Actually, the other study that we mentioned was the one that Dale just talked a little bit more about, where he actually got paired samples of feces and hide, or again, one dung lock from the hide of an animal, and in that data he wasn't able to demonstrate a correlation between those two statuses, but there, in fact, is--as Dale pointed out, the sensitivity of the hide sampling in that case was so low as to make correlation--the failure to demonstrate correlation not unexpected.

But we are--to make it clear--we are modeling simply those cattle coming in that have 0157 in their intestinal tracts, and we're using that as the indication then of their likelihood of becoming initially a contaminated carcass.

And I guess--let me also just comment a little bit on the combo bin prevalence issue. I think you've, Dane, have identified the main different there, is that we're talking about surveillance data in that case that needs to be substantially adjusted for the sample size collected from each of those combos that the prevalence was estimated from. I think the same thing applies to our ground beef sampling evidence, and that's what we've attempted to do in our comparison between what the model would predict from taking a similar sample, to what the FSIS sample size is for ground beef as well, because, as we've pointed out, maybe it's over 80 percent of the grinder loads are contaminated. You take a 25-gram or 325-gram sample from that grinder load at the levels of contamination that we are modeling, we can demonstrate that we would get about the same number of positive samples, is what FSIS has been getting, because of the low likelihood of actually getting an organism in the sample. So the data have to be adjusted for that phenomenon of sample size and sensitivity of the tests that are used.

Basically, the representativeness of that one sample is indication of what the status of that whole grinder or combo bin might be.

Did I help you on your question then?

DR. ROBACH: If I could just--Mike Robach again. Just one more point here. We've seen a lot of numbers this morning and a lot of flow charts, and so I am easily confused about these things. But from what I understand, and let's just take, for example, feedlot animals coming in, the most likely scenario is that you've got 13 percent of your animals that are going to be presented to the plant that are going to be shedding 0157. And of those 13 percent then entering, between 30 and 33 percent will contaminate themselves during--they will self-contaminate themselves during the process; is that correct?

DR. EBEL: Yeah, that is correct. And if you summarize the other routes of contamination, we get about a -40 percent of the incoming prevalence becomes initially contaminated at dehiding.

DR. ROBACH: Because we have 8 percent. Those that may not be shedding, 8 percent will be contaminated by adjoining animals?

DR. EBEL: Right.

DR. ROBACH: Thank you.

MS. OLIVER: Bill?

DR. SPERBER: Just a couple of quick observations. I'm Bill Sperber from Cargill.

I don't think we should get too excited about the fact that combos might have 0157 in them. If you look back to the surveillance data from the past 5 years, in the first 3 years of FSIS's survey, 16,500 samples, they had an incidence rate of about 0.1 percent, 1 sample in 1,000 contaminated. If you assume--these were 25-gram samples. If you assume one organism in the positive sample, that calculates out to 1-0157 per 100 pounds of ground beef. So go back 2,000 pounds in the combo, that's 20 cells in the combo. So we can't go very far down that road before we run into policy decisions and that sort of thing.

True, 0157 is an adulterant, but it's an adulterant in the sample size. It's not an adulterant in the combo or in 1 million metric tons of beef produced a year per plant, that sort of thing.

One brief comment on Dr. Hancock's observation on most probable numbers. In my experience I've done some direct comparisons on MPNs versus petri dish methods for coliforms, and CFUs on petri dishes are within a factor of 2 from the MPN geometric means. The trouble with MPNs is you have a much greater variability. The 95 percent confidence levels are very broad compared to direct plating. So with coliforms it's within a factor of 2 CFUs on petri dishes or higher, and part of that is due to the fact that using VRB, you can recover some coliforms that you don't recover in the AOAC-MPN method, which uses laurel sulfate broth that's inhibitory to some coliforms.

So in principle I think MPNs and other types of quantitation are fairly close together when you look at geometric means on many observations.

MS. OLIVER: Thanks.

DR. HANCOCK: Can I respond to that? Could I respond to that briefly?

MS. OLIVER: Go ahead, but do it briefly, because we have several other questions to cover.

DR. HANCOCK: While I do tend to agree that it might be so for some dominant organization in--like coliforms where they're the dominant organisms, I doubt that it's true for something that you are trying to detect amongst huge competing flora that outnumbers at 10,000 to 1, and that's where--in fact, the only way to test it would be to do a dilution series of known concentration in a background flora, and see if your theoretical and your observed agree fairly well, and I don't know of anybody that's done that.

MS. OLIVER: Jim, and then--

DR. ANDERS: Jim Anders, North Dakota Health Department.

I just have--I'm having--someone just said there were lots of numbers given out, and that clearly is--one thing, just before I came down here I had gotten an e-mail with a report that--and I didn't bring it with me, but it's confusing to me. It said that they now were saying that over 50 percent of all cattle had 0157:H7 in that report. I come down here now. Now we're talking about going into these slaughterhouses, that only 11 percent of these are contaminated. That in itself is confusing to me, but I have a question about sampling size that maybe is--

DR. ROBERTS: Well, let me just answer that first

question first. I mean, that was the data that was looking at--within a particular herd in the highest season of shedding, they could be as high as the number that you quoted, whereas we're looking at annual averages.

DR. POWELL: Is that hide data--Mark Powell--the report that you're referring to--

DR. ROBERTS: I don't think so.

DR. POWELL: --is that hide prevalence?

DR. ANDERS: You know, I really don't have--I mean clearly--the way I read it was, is that all of these animals were contaminated.

DR. POWELL: The difference is important in that we're not measuring or incorporating the link between hide prevalence and carcass. The only link that we have, and one that we've asked the Committee to focus on, is how can we better establish the link among the GI, the hide, and the carcass status? This right now is the link that we are using because it's the only one specific to 0157 in the published literature that we are aware of. It is from another country, and we are worried about using it for that reason. We would wish that there were data available that could help us improve those linkages, but if it is hide prevalence that you're discussing, we are not modeling the linkage between the hide and the carcass status. We modeled the linkage solely between the GI status of the incoming animals and the carcass status.

DR. ANDERS: Thank you. I do have another question thought, and thank you--hopefully that cleared that up. I'll take a look at that when I get back, and see exactly what they were talking about.

But I have a question about sampling, and clearly I'm not sure--in this model, okay, we go through this model, at the time that we're actually checking to see if the meat is contaminated or the carcass is contaminated, I understand that most of these studies have been done with 13 samples at 25 grams each, or 325 grams. Is that correct, and--I guess my question is this: if it were--if we could show that by testing more samples, or even at more grams, that was higher, would it affect this system, because that's an important issue here because--let me give you a little background.

If your own laboratory, the USDA Laboratory, I believe in Athens, Georgia, I was to a seminar about a year ago, and they were telling us that, for instance--now we're talking about foodborne outbreaks, of course, but they're taking the meat, and they said that you should take--that there was a significant difference between 15 samples of 50 grams and 30 samples of 50 grams if they were to try to isolate Salmonella of 0157:H7. If we're talking--if we're basing everything on 13 grams--13 samples at 25 grams, and they're talking that to really get the right numbers, you should be doing as many as 30 samples at 50 grams, I guess I'm questioning whether that would make a difference in this model?

DR. POWELL: We'll be getting into the samples that are taken from ground product in the afternoon, but in all cases we're making the distinction between the apparent prevalence, based on the nominal rates from the reports, and the adjusted prevalence where we have taken into account test sensitivity and sample size. So when we're talking about true prevalence, we have taken into account

sensitivity and sample size as opposed to the nominally reported rates.

MS. OLIVER: We'll go to Isabel and then Paul, and then after that we're going to break for lunch. Isabel?

DR. WALLS: My name is Isabel from National Food Processors Association.

And this question I think is really for Eric Ebel. I want to go back to the previous presentation and pick up on a comment that Dale Hancock made about the sampling. I think you indicated that the sampling was seasonal, that half of all the positives occurred at one sampling time in the warmer months. And I want to know if seasonality can be built into this model?

DR. EBEL: Well, yeah. This is Eric Ebel.

As I responded to Dale, we would like to do that. We do have data that we can stratify, to some extent, by season, and we think that the seasonality is in the within-herd prevalence. Again, we think that probably the proportion of all herds that have 0157 within them stays pretty constant through the year, but we can see seasonal fluctuations in the within-herd prevalence. And, of course, the issue is how do we model that from one season to the next? But it can certainly be done.

DR. POWELL: Mark Powell.

Just as an add-on, again, we have seasonality at the beginning. We had data that would allow us to model seasonality at the beginning of the process on the farm and at the end in this epi. But unless we can model seasonality between there, it would be--we would not be able to incorporate that in the full model, okay, because there may be seasonality in preparation, transportation, distribution, slaughter, and those right now are treated as annual national averages. So we have to treat, even where we have data that we might be able to model at a seasonal or a regional scale, we have to go to the lowest common denominator for the full model.

MS. OLIVER: Isabel, did you have any other questions?

DR. WALLS: No.

MS. OLIVER: Okay. Paul?

DR. MEAD: Paul Mead with CDC. I just have a--I hope a very straightforward question concerning your assumptions about carcass evisceration. And if I understand this correctly, your assumption is that when the intestine is ruptured in the process of slaughtering, that the level of contamination is similar to the level you get with dehiding, and that the area contaminated, as I understand, is really just, on average, an inch or to in each diameter. And not being one who has been in a lot of slaughter plants, I nevertheless have this notion that somehow splitting open the gut is a bit more catastrophic event than that--

DR. ROBERTS: Well, they try not to split it open.

DR. MEAD: Right. Well, I understand that, and that gets the issue of how commonly this happens. But I think the reason I bring it up is, I guess, there are some who are concerned that it's--that these rare, slightly more catastrophic events may really be quite important in terms of introducing high levels of contamination that may in fact ultimately be more likely to lead to human illness at the far end of this model.

And I so I guess my question is just how good are

the data leading to these assumptions, because it seems to me they may have a big influence on your model, speaking from a completely naive standpoint.

DR. ROBERTS: Now, I agree that that's a point well taken. I mean, you try to put all the important events that you can plausibly have any sort of data for into your model, and so maybe that only happened 1 in 1,000 or 1 in 10,000 times that you would have more global breakdown of the gut. Rather than just a little knife nick, you'd maybe have the whole esophagus cut into or something or more of an evacuation.

And then you'd also need to model--since that would be a noticeable event that you would definitely have clean-up procedures for, then what would be the impact of the clean-up procedures as well. So we would definitely welcome any data that anybody knows of that they could submit to the docket on this particular issue.

MS. OLIVER: Paul, did you have any other questions?

DR. MEAD: No.

MS. OLIVER: Okay, thank you.

Before we break for lunch, I have two announcements and that is, there were a number of people over the last two days who had asked questions about reimbursement either from the last meeting or from this meeting. Right before lunch Karen Hulebak and Kathy DeRover will be available, Karen for questions and any reimbursement for the last meeting, and Kathy for questions on this meeting, so you can stop.

And then we're going to break for lunch for an hour, come back about 1:10. Thank you.

[Whereupon, at 12:07 p.m., a luncheon recess was taken to reconvene at 1:10 p.m., this same day.]

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

(1:16 p.m.)

MS. OLIVER: I'd like to get started. We're going to take 10 minutes of questions after each of the sessions this afternoon, rather than the 15 minutes for this morning. Then we'll go into the questions for the Advisory Committee, and Mark Powell will lead that session in the afternoon.

And we know that the time will be limited and cut short a little bit. I know some of you will have flights, but for those of you who want to have input, we'll go till 5:30 for those who want to stay and have additional input for the afternoon. And then I'll introduce the session again later.

The first session this afternoon will be Wayne Schlosser on preparation, and Karen Hulebak will once again give the introduction on the questions to keep in mind during this presentation. Thank you.

DR. HULEBAK: Okay. For preparation, keep in mind the following two questions. Rather than modeling beyond the last point where validation is currently possible in raw ground beef, would it be preferable to consider simply a proportional relationship between the prevalence of 0157 and raw ground beef and the incidence of illness due to raw ground beef?'

Second. How do we define a plausible frequency distribution for extreme time/temperature handling

conditions in the absence of data?

DR. SCHLOSSER: Hi. I'm Wayne Schlosser.

In your handout I have removed two of the slides, Slide 45 on page 23, and Slide 62 on page 31. And it does seem like a lot of slides, but I can assure everyone that we will get through these in 45 minutes.

In previous presentations we have seen how we model the presence of E. coli 0157:H7 in cattle on farms, during transportation, in markets, and during the conversion of cattle to beef carcasses. In the preparation segment, either trimmings or whole carcasses are converted to ground beef.

This is an outline of the subjects we'll be covering today, and today, as with earlier segments, we will simply say 0157 is an abbreviation for E. coli 0157:H7.

The purpose of the preparation segment is to determine the number and extent of human exposures to 0157 from prepared ground beef products. This segment models beef from slaughter through grinding and distribution to preparation.

As outlined in the initial presentation on the project, the scope is limited to assessing consumer exposure to 0157 in ground beef. Although there are many other sources of 0157 other than ground beef to which consumers are exposed, these sources will not be modeled. Furthermore, simulation of how contaminated ground beef may lead to contamination of other products is beyond the scope of this model.

The preparation segment models the growth, decline and dispersion of 0157 for each of four types of ground beef products: ground beef that's intended for use as hamburger in homes or within institutions, and ground beef intended for use as an ingredient in beef-based products such as meat balls or meat loaf within institutions and within homes, ground beef which is intended for use as an ingredient in dishes which require intensive cooking, and granulation of the ground beef such as chili or spaghetti sauce is not specifically modeled.

The output from the preparation segment consists of the number of contaminated servings and the distribution of bacteria within those servings. These are national estimates. The range of values returned reflects our uncertainty about the actual number of contaminated servings and the concentration in those servings.

Preparation segment is a multi-path model that simulates grinding, distribution and preparation of ground beef for particular product types and locations. A complete model simulation consists of all combinations of product types and locations. This approach allows the entire model to calculate total exposures in the population as well as allow for more rapid evaluation of possible mitigation strategies.

This segment is designed to separate our uncertainty about values and distributions from the variability inherent in any biological system. As such it consists of three separate models: growth, cooking, and consumption and exposure. These three models are then processed sequentially to provide a distribution of exposures. Because of the complex structure of the model which requires summarizing sub-module outputs before simulating the next sub-module, and the large number of

iterations needed to accurately model ground beef consumption, we employ the Visual Basic for Applications Add-in to the Excel and At Risk computing environment.

This is a simplified diagram of the preparation segment. Input from slaughter and data on consumption determines the initial number of organisms in a serving. The effect of growth and cooking is determined by additional factors and added to the initial number to arrive at the final exposure dose. Multiple iterations through a single simulation give us the frequency of different exposures for a given set of uncertainty inputs.

The preparation segment relies on two types of input variables. Product fraction inputs determine the amount of product that goes into each pathway, and concentration inputs then determine the amount of bacteria present in the product.

These are some examples of product fraction inputs. All product fraction inputs reflect uncertainty only. For example, there is a certain proportion of hamburger that gets used in the home, but we don't know exactly what that proportion is.

These are some examples of concentration inputs. Concentration inputs generally reflect both uncertainty and variability. For instance, we know that the time hamburger is stored in the home varies from minutes to days. This represents the variability of storage practices. Additionally, we are uncertain as to the proportions of hamburger that are stored for the various times.

As we have seen, some of our inputs will incorporate uncertainty only, while others will incorporate both uncertainty and variability. Our final distributions are reflective of both the uncertainty and variability of the underlying distributions.

The growth process of the preparation segment simulates the effect of times and temperatures on the numbers of 0157 bacteria in hamburgers and ground-beef based products in homes and institutions. The output is a frequency distribution that describes the variation of logs of growth expected for various combinations of times and temperatures.

Additional frequency distributions describe the uncertainty attendant with the estimate of the original distribution by illustrating the effect of assuming less compliant and then more compliant processes.

Beef trim and the subsequent ground beef is subjected to a variety of storage conditions in the continuum. Ground beef may be stored under ideal conditions in one part of the continuum and subjected to extremes of time and temperature in another part. The amount of growth that takes place is dependent on the storage temperature, the length of time the product is stored and the thermodynamics of the product, which then influence the internal product temperature. We model on the temperature and time of storage. For modeling purposes, we have assumed that the storage temperature of the product is the same as the internal product temperature. This is consistent with the Food Code published by FDA and adopted by many states, which bases correct storage temperature on internal product temperature. The percent of non-compliance and the extent of non-compliance with the Food Code represent elements of uncertainty in the model.

Growth equations have been developed to predict growth of 0157 given parameters of time, temperature, and possibly pH, sodium chloride content, and other variables. One set of equations was developed by Buchanan, and it was later incorporated into the pathogen modeling program available from ARS. Another set of equations was subsequently developed by Marks.

Walls conducted a comparison of predictions from the pathogen modeling program with observations of growth of 0157 in ground beef, and concluded that the pathogen-modeling program offers reasonably good predictions of growth in raw ground beef.

Since the Marks equations were developed after the Walls comparisons, we compared the predictions from the Marks equations with predictions from the pathogen-modeling program and the Walls' observations. This chart of the predicted lag period durations show that the Marks' equations also gave reasonably good predictions. Also the Marks' equations used temperature as the only parameter. This is important, because such a parsimonious model can be used in a wider variety of scenarios with less uncertainty regarding unknown inputs.

This chart shows the predicted generation times, and this chart shows the predicted times for a 3-log increase of organisms.

Thus, the following sets of equations are used to predict growth of 0157 in ground beef. LPD here is the lag period duration. GT is generation time. And MPD is maximum population density.

Ground beef is stored in a variety of ways. The growth response of 0157 suggests that we're not generally interested though in modeling refrigerated storage. Thus, the critical factor in determining the amount of growth of 0157 in ground beef is not the time of storage, but rather the time of storage at temperatures out of compliance with the Food Code, that is, above 5 degrees Centigrade or 41 degrees Fahrenheit.

Modeling compliance with Food Codes requirements entails modeling both time and temperature as linked variables. Since the Food Code allows the product to be above 5 C for up to 4 hours, it is possible for ground beef to be stored at temperatures that would allow for growth of 0157 and still be stored in compliance with the Food Code. Thus, we model ground beef stored in compliance at temperatures from 5 C to 35 C, and at times from 0 to 4 hours.

In addition to being uncertain about the probability of ground beef being stored in compliance with the Food Code time and temperature requirements, we are also uncertain what form such compliance or non-compliance may take. There are obviously many combinations of time and temperature to which a product can be exposed. Even if we knew the distribution of these combinations with certainty, we would still be face with a great deal of variability in the storage conditions of ground beef. Unfortunately, we don't have data that suggests how ground beef that is in compliance is stored. Under such circumstances we would normally model these variables with the least informed distribution possible, which is a uniform distribution. Nevertheless, we can make assumptions about how these variables might be distributed, and evaluate the effect of

those assumptions on the model.

This chart shows the different types of compliance scenarios modeled for temperature. Institutional ground beef considered in compliance was modeled at temperatures from 5 C to 35 C under three different scenarios. In the first scenario, the frequency distribution for the storage temperature of ground beef was skewed toward 35 C and the time was skewed up toward 4 hours. We designated this "Least Compliant." In the last scenario the frequency distribution for the storage temperature of ground beef was skewed toward 5 C and the time was skewed toward 0 hours. We designated this "Most Compliant." The middle scenario used uniform distributions. Thus, any temperature from 5 C to 35 C was considered equally likely, as was each time of storage from 0 to 4 hours. This chart shows the different types of compliance scenarios modeled for time. Time and temperature scenarios are correlated within the model. Less compliant temperature scenarios correspond with less compliant time scenarios.

Ground beef stored out of compliance with the Food Code would be stored at internal temperatures greater than 5 C for longer than 4 hours. Again, we are uncertain as to the distribution of storage times and temperatures in non-compliant scenarios. Therefore, we modeled three different scenarios in a method similar to the one used for compliance storage.

This chart shows those different types of non-compliant scenarios modeled for temperature. Non-compliant time scenarios were handled in a similar manner, with possible times ranging from 4 to 10 hours. Again, with compliance scenarios, time and temperature are correlated. Less compliant temperature scenarios correspond with less compliant time scenarios.

Although the frequency of non-compliance in the home is modeled differently than the frequency of non-compliance in institutions, the distribution type of non-compliance is modeled the same for both home and institutional users for a given scenario. Thus, when we model the least compliant scenario for institutional users, we also model the same scenario for home users. The effect of linking these two scenarios is to increase the final uncertainty in the model.

The growth portion of the preparation segment assumes that ground beef is subjected to 6 opportunities for time and temperature non-compliance. At each of these opportunities an individual time and temperature is modeled for the product. Growth is then modeled for 6 sets of 64 pathways for a total of 512 separate pathways. A pathway set consists of one pathway assuming compliance at all 6 stages, and 63 pathways assuming lack of compliance at each combination of the 6 stages. Each set is then replicated using "Least Compliant", "Most Compliant" and "Uniform" assumptions about the degree of compliance or non-compliance. These three sets are then replicated for homes and institutions.

Since there's not sufficient data to construct a completely accurate model of the growth of 0157 in ground beef, it is necessary to make assumptions about how 0157 reacts to certain environments and how ground beef products are handled. The model assumes that as a product moves from one stage to the next, the internal temperature of the

product is achieved immediately. In reality the outside of the product would reach temperature first and the inside of the product last. To construct cooling curves, however, would require knowledge of additional variables that we do not have. The result would be a much more complicated model, would not be any more useful because the underlying assumptions would be arbitrary.

The model assumes that all 0157 strains exhibit the same growth characteristics regardless of the ground beef product therein. It further assumes that temperature is the only significant variable that predicts growth. We do know that factors other than temperature also influence the growth of 0157. Nevertheless, the simplification is necessary for modeling.

It is reasonable to assume that 0157 bacteria exposed to significantly different storage conditions would need additional time to adjust to those conditions and enter into a rapid growth phase. Nevertheless, we have chosen to model the lag period duration as a cumulative percentage that begins at 100 percent and decreases as product is subjected to varying temperatures at the different stages along the continuum. This is a simplifying assumption that keeps us from needing to make additional assumptions about when to restart calculations for lag period duration.

Gill reported that frozen patties from manufacturing and retail plants generally had lower log mean numbers of *E. coli* bacteria than chilled patties. It was also noted, however, that the process for production of chilled patties was distinct from the process for frozen patties, and that the chilled patties may have had opportunities for bacterial growth not experienced by the frozen patties. He also noted that in his discussion, that freezing is likely to produce only small reductions in the number of bacteria. We have thus made the assumption that freezing has no effect on bacterial numbers.

Gill reported on increases of total bacteria, coliforms and *E. coli* bacteria in beef trimmings at slaughter plants, and the subsequent ground beef in retail establishments. Using those results, we calculated expected values for *E. coli* bacteria in beef trimmings collected at slaughtering plant and for ground beef on display at a retail outlet. The difference in expected values between these two sites was .25 logs.

Gill also reported on increases of total bacteria, coliforms and *E. coli* bacteria in hamburger patties from patty manufacturing plants and from retail outlets. Using these results, we calculated the difference in the mean logs for the manufacturing plants and for the retail outlets, and the difference in these two sites was .57 logs. This was most consistent with a compliance scenario that was skewed toward the left or toward the more compliant.

We thus chose to model compliant times and temperatures as truncated exponential distributions. An exponential distribution requires only a single parameter, the expected mean. For storage time we set the mean at 1 hour with a lower bound of 0 and an upper bound of 4 hours. For temperature we set the mean at 5 C with a lower bound of 0 and an upper bound of 35 C. We further modified the distribution so temperatures below 5 C would equal 5 C. This was necessary to avoid calculation errors as the temperature reached 0.

Representative surveys of actual storage practices of ground beef and ground beef products at all stages of the continuum in the US are needed to validate assumptions regarding frequency and degree of non-compliance. Also, enumeration of 0157 bacteria grown in a variety of ground beef products under varying conditions will allow construction of better predictive models. Such research may also identify high-risk items that can then be more closely monitored.

The cooking process of the preparation segment simulates the effect of cooking in hamburgers and ground beef based products in homes and institutions. The output is a frequency distribution that describes the variation of log kill expected for various cooking temperatures. Two additional frequency distributions describe the uncertainty attendant with this estimate by illustrating the effect of assuming less compliant and more compliant processes.

Nearly all ground beef is consumed cooked. Effective cooking is dependent on the cooking temperature, the storage temperature prior to cooking, and again, the thermodynamics of the product. We model the effects of both the cooking temperature and pre-cooking storage. Rather than modeling the thermodynamics of the product, we have assumed that certain processes will lead to certain internal temperatures of the product. The temperature to which ground beef products are cooked is dependent on a variety of factors. We model cooking temperature based on the degree of compliance with the Food Code for institutional users. For home users we estimate cooking temperature from results of surveys that capture consumer cooking habits which are based on visual cues. These visual cues then correspond to a range of actual temperatures.

Juneja determined the number of surviving 0157 versus the internal temperature of hamburgers inoculated with an initial load of 6.6 logs of bacteria. Internal temperature of the hamburgers ranged from 56 to 74 C. The log of the surviving 0157 was then measured, and resulted in the linear regression equation shown here. Juneja noted that 73 percent lean ground beef patties of 100 grams, cooked to an internal temperature of 68, would have a 4-log reduction of a 5-strain cocktail of 0157.

This is consistent with a report by Jackson that 78 percent lean ground beef patties of 114 grams, inoculated with 6 logs of bacteria and cooked to an internal temperature of 68, would have about a 4.1-log reduction with a standard deviation of 0.5 logs.

Semanchek reported variability in heat resistance among 3 strains of 0157, and concluded that exposure to different environments may select for resistance to sub-optimum conditions or subsequent stress. Also, Jackson reported that the response of 0157 to cooking, appeared to be related to original storage temperatures.

Juneja has demonstrated the linear relationship between cooking temperature and the log reduction of 0157 in ground beef. Jackson also demonstrated this linear relationship, and the data also includes the effect of storage conditions on product before cooking.

Oh, Jackson did not report on the effect of cooking at temperatures greater than 68.3. We extrapolated the effect from these higher temperatures in the following manner. To predict a reduction of 0157 at temperatures

above 68, we assume a linear relationship in accordance with the report from Juneja. Using this assumption, we conduct bootstrap sampling for each of the 9 Jackson pre-treatments, using the mean log reduction and standard deviation to create simulated data points. Since Jackson reported results based on 6 data points for each of the 27 pre-treatment and cooking temperature combinations, we created 6 points for each simulated pre-treatment and cooking temperature.

From these data points, 18 for each pre-treatment, we estimate the linear regression parameters, the y-intercept, the slope and the standard error of the y. Each iteration resulted in new linear regression equations for each of the pre-treatments, depending on the 18 simulated data points. These different equations, with their expected values and standard errors, were used to predict the log reduction for temperatures up to 77, which was the highest temperature at which log reduction was calculable by the Juneja equation.

This chart shows the comparison of the predictions of the Juneja linear regression equation with the output of the bootstrap model, including 95 percent confidence limits for storage at 3 C for 9 hours.

We determined the internal product temperature of hamburgers prepared in institutional settings to be a function of compliance with the Food Code. The Food Code requires that hamburgers or other product containing ground beef be cooked to an internal temperature of 68. We therefore constructed the model to simulate the effect of cooking in cases of compliance, 68 and above, and in cases of non-compliance below 68.

As with temperatures in the growth model though, it is considered that some hamburgers non-compliant, may have reached temperatures close to 68, while other non-compliant hamburgers may have reached much lower temperatures. And some hamburgers that are in compliance, may only have just reached 68, while others may have reached much higher temperatures. The actual frequency distribution of cooking temperatures may have a significant effect on the log reductions observed in the model. So we again determine both the uncertainty and variability of log reductions through cooking.

Non-compliance with cooking requirements in institutions is based on consumption information from the 1995 Continuing Survey of Food Intake by Individuals. Institutional hamburgers considered in compliance were modeled at temperatures from 68 to 77, with three different scenarios.

In the first, the frequency distribution for the pre-treatment of hamburgers was skewed toward those pre-treatments that were considered most abusive. The frequency distribution for temperature was skewed toward 68. This was designated least compliant.

In the second scenario, the frequency distribution of pre-treatment of hamburgers was skewed toward those pre-treatments considered least abusive. The frequency distribution for temperature was skewed toward 77, and the scenario was designated most compliant. The third one used uniform distributions. This chart shows the three cumulative distributions for each of the scenarios for compliant institutional hamburgers.

As with compliant hamburgers, those considered not in compliance were modeled with three different scenarios. In the non-compliant scenarios, temperatures ranged from 54 to 68. This chart shows the three cumulative distributions for each of the scenarios for non-compliant institutional hamburgers.

We consider it less likely that hamburgers will be cooked to a given internal temperature in the home than in institutions. Institutional cooking is subjected to regulation regarding product temperature, and institutional cooks are more likely to have access to accurate measurement devices. Thus, in the home another method of determining internal product temperature for the purpose of modeling is used.

Klontz distinguished between two categories of hamburgers, rare and medium, defined as at least some pink in the middle, and medium well and well, defined as no pink. We used information from the 1995 Continuing Survey of Food Intake by Individuals to model the fraction of hamburgers served rare or medium. Unfortunately, there is not as good a correspondence between these designations and internal product temperature as we would like.

Lu reported on a study in which two replicates of five previously frozen hamburger patties were cooked to internal temperatures of 68, 71 and 74 degrees. In one replication, patties cooked to 68, 71 and 74 would have been considered as cooked medium. In the other replication, hamburgers cooked to 68 would have been considered as cooked medium. Thus, there is considerable variability in the final appearance of cooked hamburgers given the same formulation and the same internal temperature.

Hamburgers considered to have been cooked to a medium degree of doneness may have reached internal temperatures of 68, or even as high as 74. Hamburgers considered rare or medium are thus modeled as having reached internal product temperatures of anywhere from 54 to 74 C.

Furthermore, for the purposes of this model, hamburgers considered medium well or well-done are considered to have reached temperatures from 65 to 77. As with institutional cooking, it is probable that the actual frequency distribution of cooking temperatures within these two categories would have a significant effect on our ability to predict log reductions.

As with institutional cooking, home-cooked hamburgers considered medium-well or well-done--what we'll considered as in compliance--were modeled with three different scenarios. Temperatures ranged from 65 to 77 in each of those, with weights toward least compliant, most compliant, and uniform. Outputs for each of these three scenarios for both rare-medium and medium-well, well-done hamburgers was captured and compared to determine if the underlying frequency distribution would have an effect on the log reduction predicted.

This chart shows the three cumulative distributions for each of the scenarios for medium-well, well-done home-cooked hamburgers. Home-cooked hamburgers considered rare or medium were modeled at temperatures from 54 to 74 with the three different compliance scenarios.

We have assumed that ground beef used as an ingredient in products such as chili, spaghetti, soup and other such products will be thoroughly cooked to an extent

that would kill all 0157 present. This is because the ground beef is pre-cooked in a granular form and then subjected to further cooking.

In products that use ground beef as a major ingredient, we have assumed that cooking practices will parallel cooking practices for hamburgers. On the one hand, we may think that consumers would be less likely to eat rare hamburger than rare meatloaf. On the other hand, we do not have data describing the distribution of cooking practices for other ground beef-containing foods.

It is reasonable to assume that many individuals cook hamburgers to higher temperatures than this model assumes. Jackson, however, did not study cooking beyond 68, and Juneja did not study cooking beyond 74. The linear relationship between cooking and reduction of the number of 0157 organisms is based on an initial concentration of 6.6 logs. This relationship predicts elimination of all 6.6 logs of organisms at around 77 C.

It may be reasonable to assume that a higher initial of 0157 may be affected not in a direct correspondence to this relationship, but rather proportional to it. In other words, if a product was originally contaminated with 10 logs of 0157, it would also achieve complete elimination of all microorganisms at about 77. Although this assumption is intuitively appealing, there is no data to support it. Therefore, we have chosen to model the reduction of 0157 in direct correspondence with results of experiments that had lower inoculums than those predicted in the model.

The purpose of the exposure process of the preparation segment is to combine input from the slaughter segment with the output from the growth and the cooking processes to determine the frequency of contaminated servings and the distribution of bacteria within those contaminated servings.

The majority of ground beef is used in hotels, restaurants and institutions. Ninety-eight percent of this product comes directly from grinders. Retail establishments use coarse ground beef and mix with it trimmings produced in-house. Retail establishments also buy case-ready chubs, which are plastic tubes filled with 5 to 10 pounds of ground beef. About 22 percent of retail ground beef includes at least some retail trimmings. A commercial lot of ground beef is modeled as a uniform distribution from 2 to 15 combo bins of 2,000 pounds each. We model a retail lot of ground beef as uniform distribution from 50- to 400-pound lots.

The Food Code specifies a holding temperature of 5 C or below for ground beef and products made with ground beef. The proportion of product considered in non-compliance is based on assuming that the likelihood of trained individuals in the food service industry allowing product to remain above 5 C for longer than 4 hours could be as high as 1 out of 100 or as low as 1 out of 10,000. We have assumed that the likelihood of untrained individuals in the home allowing product to remain at temperature above 5 C for longer than 4 hours could be as high as 1 out of 10 or as low as 1 out of 1,000.

The Code also requires that hamburgers or other products containing ground beef be cooked to an internal temperature of 68 C. Uncertainty about the level of non-compliance with this requirement for institutional cooking

is based on the Continuing Survey of Food Intake by Individuals, and it is modeled as the beta distribution shown here. Modeling of non-compliance cooking within the home is also based on the CFSII, and modeled as the shown beta distribution.

Ralston conducted an analysis of the 1995 CFSII which was based on reports of about 15,000 individuals and covered about 30,000 days of observations. This table shows consumption of hamburgers at home and away from home for four different age categories. This tables shows consumption of ground-beef products at home and away from home for the four age categories.

The presence or absence of clustering of 0157 in ground beef is an important but unknown factor. If CFUs tend to be clustered, we would find fewer exposures but larger doses. And we'll make the assumption that clusters of CFUs would be randomly distributed in contaminated ground beef.

Although there is no data to support the presence or absence of clustering of 0157 in ground beef, we assume that clustering follows a binomial process. In other words, the probability of a CFU of 0157 being clustered with another CFU of 0157 is fixed but unknown. The number of 0157 CFUs in a cluster will then vary and is directly calculable if the probability of clustering is known.

In the model, the number of clusters is calculated by dividing the number of CFUs by the modeled mean cluster size. The mean cluster size is equal to the mean of the negative binomial distribution plus 1. The negative binomial distribution returns the number of clustered CFUs before a non-cluster event. The number of 0157 CFUs in each cluster is then simulated and summed using a negative binomial distribution.

This again shows the structure of the preparation segment. Remember that outputs from growth, consumption, and slaughter are combined to develop a frequency distribution per dose of exposures. One simulation of the model gives results for a given set of uncertainty inputs.

Output from the grinder section of the preparation model suggests that there are about 85 million potentially contaminated servings produced in the U.S. annually. About four-tenths of a percent of these, or 375,000 servings, are predicted to have at least 1 organism present at consumption.

This chart shows the log of the dose along the x axis and the log of the number of exposures along the y axis. About 40 percent of the exposures are to 1 organisms. About 10 percent of the exposures are to doses of 1,000 or more organisms.

Initial uncertainty analysis in the model has been accomplished by first identifying the uncertain inputs. These were generally the proportion of non-compliant events and the shapes of frequency distributions. The model was then run with uncertain inputs set at the most likely values and then with the uncertain inputs set at upper and lower bounds.

This chart shows the most likely exposure curve we saw a couple of slides back, along with the exposure curves resulting from simulations at the upper and the lower bounds of our uncertainty distributions. As you can see, there is a considerable amount of uncertainty within the model.

The preparation segment of the process risk model is complex and resource-intensive. Nevertheless, this segment can represent only a simple view of reality. As we fill in data gaps, we get closer to modeling reality. Obviously, if we had perfect data for every input, we wouldn't need to do a risk assessment; we would know the risk. But one of the products of the risk assessment will be to help us better identify where the data gaps are and how we can fill them.

Thank you for your time. Questions?

MS. OLIVER: Okay. We'll take 10 minutes of questions now, so if the Committee or any of the invited experts has--Dane?

DR. BERNARD: Thank you. I thank you for your presentation. There are a couple of things I need personally a little clarification on, though, if you don't mind.

As I remember the growth data--and Dr. Walls can help me out with this--0157 doesn't grow at all below somewhere between 7 and 8 degrees C. Was that accounted for in your predictive models? Your tables here show 12 C, but it is not linear down to 5 C, which is the Food Code-recommended storage. So when you talk about non-compliant storage with Food Code provisions, and even at 12 C, what's the lag time? 15 hours.

At 8 C, what would the lag time be? I think it would be something probably much longer than that. So in your modeling, was that accounted for as you predicted what the population might have been? Did you account for the fact that there is no growth at all below somewhere between 7 and 8 C?

DR. SCHLOSSER: What we do is we draw from a distribution that goes continuously from basically 5 C up to 35. So as we draw from 7 or 8 or 6, I think actually it predicts some growth, but the lag period in the generation time is very long, basically no growth.

DR. BERNARD: You know, just my--I'm not a modeler, but personally I think it's not a fair assumption to look at the Food Code as your null hypothesis in terms of storage conditions, where you can begin to have a problem. I think you have to look at what the model says, what the actual observed growth says, and begin from there.

In addition, while you've presented some very interesting data in terms of survival from cooking conditions, as I remember the CDC data--and Paul is better to comment on this than I--pink hamburgers still come up as a risk factor, whereas restaurant-cooked hamburgers dropped off the last data set as a significant risk factor.

In addition, some of the outbreaks that have happened--and possibly Dr. Kobayashi can comment on this as well--reports that we got back on the degree of undercooking indicated that we didn't miss it by 1 or 2 degrees C; we missed it by a mile. So those slightly undercooked situations don't appear to be showing up as a risk factor. It's the drastic undercooked situations that appear to be showing up as a risk factor.

So I'm wondering if that's consistent with the predictions that you've made here in terms of, A, potentially contaminated servings, and, B, potential exposures from those contaminated servings.

Thanks.

DR. SCHLOSSER: As we look at probably individual servings of hamburger, we see a relationship. As we cook hamburgers only to 54, we get a very low reduction of 0157. As we begin moving that up higher and higher, we get more. What the model does is draw from a continuous distribution of hamburgers on each iteration, things that might occur in the population. And we're up around 68, we get pretty good reduction. As we drop down to 54, we get very poor reduction. So, basically, the rarer or the pinker it is, the more problems you would have.

DR. POWELL: Mark Powell. I wanted to respond to Dane. I'm not sure if Wayne responded to all of the parts of your question, as I understood it. Wayne discussed how he is modeling the consumption essentially of the lag phase duration, so that if a product is at a temperature at which growth would occur, even if it is in compliance with the Code, it would have to be held at that temperature for a sufficient time for 100 percent of the lag phase duration to be consumed prior to the initiation of growth.

DR. BERNARD: May I?

MS. OLIVER: Yes.

DR. BERNARD: I guess what I'm saying--Dane Bernard--I'm not exactly in agreement right at the moment with the assumptions that you started from to make your calculations. In terms of where you started, I think it's a great leap in logic to say that lag period is shortened by any storage outside the Food Code-recommended conditions, which I think is what you indicated that you were modeling.

There are a lot of assumptions here that I think need additional study and might be providing maybe much more uncertainty in your predictions than we would actually need. If you even look at the information we have today in terms of growth characteristics of the organism, I think we could be a little more accurate in the predictions that we're getting. I mean, you may be exactly accurate now. It's just that I have some questions about the ongoing assumptions and I'm personally not in agreement with some of them.

DR. SCHLOSSER: One of the things the model will allow us to do is set temperatures at particular settings and then let us see what the effect is that the model is predicting. We haven't done it for those particular temperatures and run it through to see, but we can do that.

MS. OLIVER: Bruce?

DR. TOMPKIN: Bruce Tompkin. In your estimates, are you considering that some of these in terms of growth, the potential for growth, the fact that there's a substantial quantity of ground beef that is sold frozen and cooked from frozen so there is no possibility, or at least the risk of growth is minimal?

DR. SCHLOSSER: Yes. We consider the effect of actually storage conditions gets introduced in the survivability of E. coli as we cook it. But we also consider a great deal of product as having no opportunity at all for growth.

DR. TOMPKIN: But are you coming up with an estimate for the percent of ground beef that is sold and cooked from frozen?

DR. SCHLOSSER: No, we don't have that, and if you have that, we could use that in the model.

DR. TOMPKIN: Okay. Can I ask one more question?

MS. OLIVER: Sure.

DR. TOMPKIN: With regard to this next to the last slide, I thought--perhaps it's a matter of how I read it, and so on, but, of course, with statistics you can go anywhere you want with it, but you've got some high numbers of E. coli 0157 and it's a question at what point will the product be spoiled. You know, there is a practical limit, I think, in terms of how high you can go with 0157 as a result of growth and the product still be acceptable and not, you know, actually be rejected and not cooked or consumed. So there is a practical limit in there somewhere.

MS. OLIVER: Chuck Haas?

DR. HAAS: Yes. I'm not clear how you got your probability of not clustering.

DR. SCHLOSSER: We assume that the probability of not clustering is somewhere between zero and 1, and we--

DR. HAAS: So you sampled from a uniform distribution?

DR. SCHLOSSER: No. We do one simulation assuming it's 0.5, another assuming it's 0.1, and the last one assuming it's 0.9.

DR. HAAS: Okay.

MS. OLIVER: John Kvenberg?

DR. KVENBERG: Thank you. John Kvenberg, Food and Drug Administration. I guess I'm going to ask basically points of clarification, but I would like to remark that I have certain reservations about the assumptions, as I think were expressed by Mr. Bernard.

The first question, under the scope of this thing, cross-contamination was not included in the scope of the study, and I assume that was the basis that this model was basically assessing the risk of hamburger, per se, is that correct?

DR. SCHLOSSER: Right.

DR. KVENBERG: Well, what's the reason for within the scope where cross-contamination is not included in your model?

DR. SCHLOSSER: For instance, if we start looking at the possibility that a food service worker is infected with E. coli and from that contaminates some hamburger, we just considered that beyond the scope of the model. It's much more complex than we're able to do in what we're doing here.

DR. KVENBERG: Thank you, okay.

DR. POWELL: Mark Powell. I just want to clarify, too, that when we correlate the model with the epidemiologic estimate we have made an effort to partition out secondary transmissions and other sorts of sources of 0157 infection, so that our effort with the epidemiologic estimate which is derived independently from the 0157 is essentially to scrub those cases out.

DR. KVENBERG: Thank you. The second question I have is I--and I ask your forgiveness for not comprehending this. Under growth factors, on slide number 17, storage temperature is equal to internal product temperature. Would you go through that one more time, because I fail to understand the temperature of storage as it relates to this four-hour period and the internal temperature of the product as it relates to growth factors because the assumption is not only is there a lag phase involved, but there's a temperature differential in the product versus room

temperature. What's the rationale under growth factors, please?

DR. SCHLOSSER: You mean why do we use that rather than trying to model the growth curve and see what the product internal temperature might be, given a certain ambient temperature?

DR. KVENBERG: Why did you make the assumption that the storage temperature equals the internal product temperature? If I understood your remarks correctly, you're basing this on the '97 Food Code that is based on four hours, with a time out of temperature at four hours. Assuming that's the ambient temperature that the product is in, how does the storage temperature or the internal temperature of the product outside of storage, if that's the point--or is this the storage temperature within refrigerated storage you're referring to here? I'm confused.

DR. SCHLOSSER: It's basically the storage temperature. We say the internal product temperature is equal to whatever the ambient temperature is.

DR. KVENBERG: Within cold storage or prior to preparation during that four hours, both?

DR. SCHLOSSER: Correct, yes.

DR. KVENBERG: Well, I think that's a flawed assumption because the internal temperature of the product certainly can't equilibrate to room temperature immediately.

DR. SCHLOSSER: Right, and when it goes into the refrigerator, it can't equilibrate to the refrigerated temperature immediately. And we thought again that that was an important simplifying assumption to make in the model.

MS. OLIVER: Okay, we'll take one more question before we move on to the next session.

Colin?

DR. GILL: The modeling of lag times is notoriously inaccurate because you'll get a different result depending on how the lag was induced. Do you know what were the conditions applying for your models? Particularly, are you talking about aerobic or anaerobic conditions? Are the cells--are you considered pH-adapted cells, cells adapted to acid conditions, or unadapted cells? And do you know what the circumstances were of inducing cessation of growth?

DR. SCHLOSSER: I don't think I can answer any of those questions. Is there anyone here that could answer those for us?

DR. WALLS: I can give the information for our model, and I can give it to you later, probably.

MS. OLIVER: Okay. Skip, if you have a quick question, we could take that and move right on.

MR. SEWARD: No.

MS. OLIVER: No, okay. We'll move on to the next session, then, on dose-response, and Peg Coleman will give that section and Karen Hulebak will introduce it.

DR. HULEBAK: Okay. During Peg's presentation, think about the following two questions. Are there sufficient data and methods available to develop a separate dose-response relationship for the susceptible sub-population? How might we validate such a curve? Is the basic envelope approach sound? Peg will describe that approach. Is it appropriate to anchor the most likely value for the dose-response; i.e., the beta-Poisson envelope?

MS. COLEMAN: I hope you have new hand-outs.

There should be six per page. I was told that they were delivered during the lunch break, or perhaps in the morning, and it would have this title on it.

Well, I am pleased to represent the team, and present to you our ideas and concerns about the dose-response assessment for this project. I should credit Chuck Haas for starting us off. I think it was in '95 or '96 that we brought him down from Drexel to start us thinking about dose-response modeling in the Food Safety and Inspection Service, and we credit his expertise.

And some of the Committee members know, then, that I have a longstanding interest in dose-response assessment, and I'm pleased to have been elected just this week as President of the Dose-Response Specialty Group for the Society of Risk Analysis. And I look forward to some beneficial cross-fertilization in the coming year with our colleagues who address similar issues for chemical and physical hazards.

The team is requesting your input on dose-response assessment, and in order to assist us with incorporating your input we're eager to learn your perspective of our interpretations of the available data. Perhaps you might suggest different interpretations or additional studies that we should consider. My goal with you is to be brutally transparent about what we think we know and what we don't know, and our confidence in alternative interpretations.

In the next hour, our focus on the dose-response assessment for 0157 is two-fold. First, transparency between science and judgment. One perspective of the available science is that no available human data from either epidemiologic investigations or controlled clinical studies is available to directly develop a dose-response relationship for E. coli 0157:H7. Of course, some data are available from which we can make inferences about the dose-response relationships for 0157:H7, and one perspective of the dose-response assessment is that of a mixture of science and judgment because we are making inferences and extrapolating from less than ideal definitive data sets.

The second focus of this talk is on uncertainty. In our judgment, uncertainty predominates the dose-response assessment for a number of reasons, including the lack of data from controlled human clinical studies and the lack of data on the dose-response relationship for more susceptible human sub-populations. However, we do recognize the importance of variability in dose-response assessment.

Variability in each aspect of the epidemiologic triangle--the host, the pathogen, and environment--and also their interactions, is important to realistically describe the complex, multi-stage process of pathogenesis. And this idea is not new to you, since the FDA has mentioned these issues to you already in describing their risk assessment work.

However, our judgment is that the available data are insufficient to permit us to explicitly model variability of host, pathogen, environment, or interactions at present. And we will turn our attention, then, to uncertainty and selection of plausible surrogate dose-response models.

I expect that if we in this room voted on the first question, are children more susceptible, that we might have consensus. Although we may believe that children are

Note the shift in the dose-response curves is not strictly a linear shift from the normal animal to the more susceptible animals, but that the shifts reflect changes both in the shape and the position of the curves. This red line is fitted to the normal animals, and this black line is fitted to animals that received a pre-treatment with antibiotics to knock out their indigenous flora. And their ID50s or the infectious dose for 50 percent of these animals shifted five orders of magnitude.

The intermediate lines represent fits for pre-treatment with antibiotics for two days, and then challenge with the pathogen three days, for days, five days. So by five days, the indigenous flora appears to have recovered enough that the animals are fairly similar to the normal animals in their dose-response relationship. These data illustrate that one true infectious dose not exist, and that the shape and the position of the dose-response curves for normal and susceptible animals differ, the ID50 in this case shifting five orders of magnitude.

In recent months, studies in the peer-reviewed literature, like those Japanese studies, came to our attention and caused us to reconsider some of our assumptions about this pathogen in the older literature. For example, we expect that as you increase dose, the likelihood of illness would increase. There was also a Stanford study that was published in Science that demonstrated increased severity of illness with increasing dose.

Many data sets from the clinical feeding trials fit a variety of sigmoidal curves, and a manuscript appearing this month in Risk Analysis includes Dr. Doyle's name on the author line and they explored a number of empirical model forms for dose-response assessment. We'll present some evidence for the importance of depicting uncertainty about the true model form, the shape and the position of the dose-response curve.

Before we ask if our modeling is defensible, we ask you as an Advisory Committee about the interpretation of the available body of evidence from the scientific perspective. Clearly, a model that is based on weak science is a weak model. As a team, we're seeking your input so that our model is transparent and is based on the most defensible scientific data available and on well-reasoned judgments.

Four possible criteria are posed in this slide for selection of surrogate models. We're going to focus pretty much on this last category which we think is probably the strongest, where we're looking at the similarities in the expression of specific virulence genes.

Other Escherichia strains are potential surrogates, obviously. But, in addition, several other related bacterial strains might be considered as potential surrogates. The genus Escherichia seemed to diverge from Salmonella perhaps 150 million years ago, and then to diverge again from Shigella only 80 million years ago. And you may be aware that the full genomes of both the comensul and 0157:H7 strains have been sequenced recently. And evolutionarily speaking, the pathogen seems to have acquired over a million new base pairs that are not detected in the comensul strain. This work may greatly impact our understanding of pathogenesis, and also our ability to

inhibit pathogenesis.

Data are available from human clinical trials for four possible surrogate pathogens--Shigella dysenteriae; Shigella flexneri; enterotoxigenic E. coli, or ETECs; and enteropathogenic E. coli, or EPECs.

Will the selection of plausible surrogates affect our risk assessment? Most definitely, yes. This slide might help to convince you. Here are the ID50 estimates for fitted models, and these are beta-Poisson models. Shigella dysenteriae appears to be the most virulent, in that half of the animals dosed would become ill at 1 times 10 to the 2nd, 200 organisms, whereas the EPECs require 7 times 10 to the 8th organisms to make 50 percent of the human volunteers ill.

The remaining surrogates, including one animal study that--actually, Chuck Haas just gave us the paper. It will be appearing in the International Journal of Food Micro, is that right?

DR. HAAS: Yes.

MS. COLEMAN: But he had also shared his last student's thesis work with us, so we had seen these data and some others, and I'm sure that will come up in the discussion. But for this point, I guess I'll just close this slide out and say that since Wayne's output from the preparation and cooking module predicts 40 percent of the positive servings with only one surviving cell, when you're extrapolating from these two extremes to the low dose region, dose-response assessment is going to be very important.

This graph depicts the data by strain from human clinical trials conducted at the University of Maryland in the 1970s, and at Stanford in the 1990s. In our judgment, these two potential surrogates represent most closely the range of possibilities based on the common virulence genes.

Shigella dysenteriae, in blue, is the only potential surrogate that routinely expresses Shiga toxin, but it differs mechanistically in invasiveness. The EPECs, in green, are the only potential surrogate that shares with 0157:H7 the locus of enterocyte effacement or the lead pathogenicity island, and also the associated pathology of the attaching and effacing lesions in the host. However, most EPECs lack the Shiga toxin genes, and so they be less virulent than 0157:H7.

So we're reasoning that those two extremes might be plausible upper and lower bounds for 0157:H7. And those data were sparse--2, 3 or 4 dose groups in each of the experiments, and 40 individuals in the Shigella dysenteriae volunteer trials, and 37 in the sum of the 3 EPEC trials.

Our focus for this final leg of the risk assessment is on three basic approaches, and each one is sensitive to assumptions. Six of us have contributed most of the work in the dose-response assessment to date, and half of us favor a simplistic bounding approach and I think all of us are hopeful that we'll generate more epidemiologic data to be able to anchor a bounding approach to outbreak and FoodNet data. But we'll describe some of those details in further slides.

Before we get into the evidence and the outputs of our models, I'll spend a little time discussing the epidemiologic evidence. There are two basic outbreaks in the U.S. that have caught our attention, the 1993

northwestern states outbreak associated with undercooked fast-food hamburgers and the '95 venison jerky outbreak.

Most of the details on this slide are probably known to the Committee. Although a direct count of the persons who consumed hamburgers in this outbreak was not available, we do have an estimate of the non-recalled patties that we presume were consumed. So though that's not a definitive estimate of consumption, it does allow us to calculate an attack rate. And it is a very low attack rate, .00037 per serving, if we're assuming that each of these million-some non-recalled hamburgers were consumed.

There were some severe endpoints with this outbreak, and I'll just focus attention for a minute on these results. We've already had discussions about the MPN method. Is it an underestimate, an overestimate? There were a couple of interesting papers at the Society for Risk Analysis that suggest that MPN may actually measure colonies or clusters and not cells, which is an interesting idea.

I also have heard through the grapevine that when these analyses were conducted, there wasn't the pre-enrichment step that we might do today to recover injured organisms. So we're not all that confident in the levels even in the raw frozen product, and the next slides will raise some additional questions.

I think the idea of dose reconstruction is probably more well-grounded in risk assessments for radioisotopes, but we certainly can look at dose reconstruction in a more formal way. We have our MPN counts in the raw hamburger. There are actually conflicting studies. Some seem to suggest that there is a decline in recovery from the frozen state, and others not. We'll have to look more closely at that.

We know from a study by Bell that undercooking was a risk factor, and that undercooking was actually fairly severe. In the Bell study, some burgers cooked under the processes that the fast-food restaurants were using were only cooked to 108 degrees F, where USDA currently recommends cooking to 160, so very light cooking. But the bottom line really is we're uncertain about what the ingested doses were in that outbreak.

So here's a slide of what we don't know. We're not certain about how good our enumeration methods are, what our recoveries are from food samples, what is the extent of clustering. And as a result, we have fairly low confidence in the estimates of ingested dose from these six MPN values. I already mentioned this. That's enough.

So this is the second outbreak, the venison jerky outbreak, and there are actually a couple of you in the room, I think, whose names are on this study. And if you don't mind my saying, the report was a little sketchy.

[Laughter.]

MS. COLEMAN: So you might be able to enlighten us a little bit, so I'm hoping that you'll do that.

For example, we had 6 confirmed cases and 5 presumptive cases mentioned, 13 individuals on a weekend retreat eating venison jerky. And the presumptive positives--there was some delay in actually analyzing the fecal samples, or perhaps in getting the samples. But 8 to 16 days after the onset of illness, you're probably not going to detect that pathogen, even if it was the causative agent of your illness. So you might include the 6 confirmed

and the 5 presumptives, and estimate a pretty high attack rate for that outbreak.

Just a couple of notes. There was a 3-year-old that was the only case that sought medical attention. There was a 9-month-old that had diarrhea, but was not known to consume the jerky. Now, here's a little bit about what we don't know. The information in the report was pretty anecdotal about consumption, and this is a quote that some individuals, some hardy soul, consumed 500 grams over the next few days. That's a lot of jerky. So, that's really all the evidence that is reported in that outbreak as far as consumption.

Now, we have two estimates of MPN, 3 per gram and 93 per gram.

He's telling me to hurry up.

You could think about these as two observations and take the mean and assume that a mean serving tells you something. But it's also possible that you really do have some samples that are low and some samples that are high, and so an interval analysis approach may be worth looking at in addition to taking a mean and looking at what that tells us about the doses that might have made people ill. So neither the last outbreak nor this one utilized a pre-enrichment step, so we're not sure if we've really accounted for all the injured cells in that count.

And these are kind of my musings about what might a 3-year-old child have actually ingested, and I guess the bottom line is we really don't know, but probably 500 grams in thousands of counts over the weekend is probably not realistic. But we really don't know if that child only had one serving comparable to a Slim Jim pack and that that was enough to make them ill.

Some common uncertainties of epidemiologic data. We generally don't know the doses of the pathogen that caused illness or those that didn't cause illness. We often don't know the serving sizes, and the attack rates as they are normally calculated don't account for variability and uncertainty, though Mark will show us some ways to do that in the next talk.

So because of that, we have low confidence for the estimation of the infective dose or minimum infective dose from these two outbreaks. And I don't think I need to make a plug to this audience for improving the multi-disciplinary nature of our outbreak investigations, but clearly we could do some case-controlled studies and bring in some more food microbiology and try and generate some data that will enhance our understanding of dose-response.

Our judgment so far is that the available epi data don't permit development of a dose-response relationship for 0157:H7. Originally, the team had expected to provide separate estimates for exposure by age interval, so we still have adults over 16 as our input for this model. The input from the preparation and cooking module comes in here. We put that value into our surrogate dose-response model and we generate an output of a number of annual illnesses per year.

The first two examples here will be illustrated in subsequent slides, and I refer you to the JIFSAN Web page for the third example. But I thought it was worth saying in an audience where risk management is of interest that some of the importance of dose-response modeling might depend on the goal of the assessment. If a risk manager isn't really

interested in the truth number with attendant uncertainty of illnesses, you might think that the dose-response model form wouldn't be important.

But even if you're just interested in finding relative risk reductions when you intervene in the process, model form can give you different answers. So you'll see an interesting example showing parameter uncertainty, and maybe a less interesting one about model uncertainty, but let's go ahead.

Clark Carrington came up with some of this philosophy for us. Parameter uncertainty is pretty well-known to the group, I think, that you can account for sampling error and measuring error in the numerical estimation procedures for fitting your model.

Scientific uncertainty is a little more philosophical. Model form is one aspect of scientific uncertainty, but this one--I think Clark coined a new term here. Analogical uncertainty refers to how good is our analogy between 0157:H7 and Shigella, or 0157:H7 and the EPECs. And so that kind of analogy is a big part of our scientific uncertainty for this process.

Bootstrapping is a common technique, and you've heard some mentions of it already so I won't go into it in great detail. But this is it, this is the data set for Shigella dysenteriae. We have 4 doses, we have 6 observations, and only 40 individuals that were sampled. But go ahead to the next slide.

Now, Mark is going to load a data file, and this is the same data set we just saw on the screen. And we're going to put in a parameter file, so this file was generated with a C-plus-plus object. Clark Carrington had worked this up first in visual basic and then hired a contractor at Maryland to help him bring it in as a C-plus-plus object. Very shortly, this will be posted on the Web for others to use in looking at model and parameter uncertainty.

When this is done cycling, maybe you can go down and change the log scale and just step through a few of these, but these are all models that fit that data. This is the low-dose region, this is 10 organisms, and we do have one observation from the Shigella data set there. And you imagine, when this curve flattens out, what that is doing to your prediction of illness at a dose of 1 organism. These all fit the data. It's pretty amazing, so this is parameter uncertainty, and the model form is beta-Poisson. It's pretty amazing.

Okay, next. Now, we have a couple of flat pictures to show you about model uncertainty. Here, we have five different model forms, and this is the observed region and they all fit the observed region well. I just changed the scale here so that you can see the divergence of the predictions when you go to the low-dose region.

He's making me hurry. Okay, that's all right.

So if we didn't account for model uncertainty, we might be overstating our confidence about what proportion of illness we would really be predicting at the low doses.

I'm sorry. I had an extra slide in there. No wonder I was confused.

There are a number of published papers, two that are mentioned here, that have looked at shigellosis as a surrogate for 0157:H7. And we'll show you some results, but we're going to spend more of our time thinking about the

approach of bounding the human data with an upper bound of *Shigella dysenteriae* and a lower bound of the EPECs.

First, we entertain an assumption of a uniform distribution between those two to reflect our uncertainty about how analogous 0157:H7 really is to the upper-bound and lower-bound strains.

We're proposing this as a validation strategy, but also a future form to generate dose-response models, and that builds on the previous idea that we--actually, this idea came first, so credit Mark Powell for this, but the upper bound of *Shigella dysenteriae*, lower bound of the EPECs. But then we're looking at a "most likely," and this is a very creative and interesting approach where we have the data from those two outbreaks and FoodNet predictions that anchor that "most likely." We could also validate with a rabbit clinical trial dose-response model, and there are other assumptions that we might be able to test.

Okay, so this is the data. This is our one slide of results for the dose-response modeling. This your average *Shigella* uncertainty, and you'll notice that it is the broadest peak out there. This does account for variability and uncertainty, and it's the only model besides maybe the epi data that does that.

This red model is the upper and lower bound, with a uniform assumption. This bright blue curve is the beta-Poisson envelope approach, the bounding approach with the anchor to the epi. And then these data--Mark will describe to you the derivation later, but these are based on FoodNet. Oh, I didn't tell you the axes--thousands of cases and the probability of illness.

I'll go through this briefly because I'm sure there will be some questions. But you could make different assumptions about exposure for the dose and the response for the venison jerky outbreak. And you can generate a cloud of points and fit a line through it, and that is exactly what this blue line is. So this is what we're saying is our most likely, and it's convenient that it has fallen right between the upper bound and the lower bound.

And if you'll go to the next slide, you'll see that this point here is the estimate of attack rate for the western states outbreak. And this is based on data from Washington State, and I think if you look at the full four-state outbreak the attack rate might be a little lower. But still you're between the upper and lower bound, and that's a pretty good anchor for epi data.

Okay, my summary slide. I probably won't get any argument that we have great uncertainty associated with surrogate dose-response models. In a sense, our most compelling bounded approaches have attempted to account for uncertainty as fully as possible. We don't really know if these models are really bounded in this way, but we also wonder if this approach might also include the dose-response models that might be envisioned for more susceptible sub-populations. I'm sure that will come up in discussion.

So I had a few slides just kind of to get you thinking about what kinds of things we'd like to hear you bring up with us, and I'm sure you have others. But what do the available data tell us about predicting illness for 0157:H7? Should we be limiting our modeling to healthy adults, since we're basing our models on the human clinical trials, and could we go farther?

If the Committee felt strongly that we really should model more susceptible sub-populations, how might we think about doing that? Should we treat the 1- to 2-year-olds separately, since they seem from the FoodNet data to be so different from all the other groups? And how do we deal with the immunocompromise in the elderly?

If we did decide to expand our family of dose-response models to incorporate all these, of course, as Mark has already pointed out, that means that our whole exposure assessment has to link in in the same way, that we would have to have consumption data for the immunocompromised. And so it's not such a simple thing to say, okay, just give us another model and go with it.

And then is a 10-fold factor enough? Do we need to think about more orders of magnitude than that, or do we put some funding into research studies to try and address the biology of the issues?

Does the approach for surrogate dose-response modeling convey attendant uncertainties sufficiently and transparently? Is the scientific evidence supporting each approach for dose-response assessment plausible?

And I want to thank especially Clark Carrington for technical assistance and use of the C-plus-plus object. And I thought I'd end with a nice view of Cranberry Lake at Christmastime.

Thank you.

MS. OLIVER: Thank you very much.

We'll take questions now for ten minutes.

Peggy?

DR. NEILL: From one Peg to another, I have a couple of points, Peg, none of which are probably going to really directly answer some of those latter questions, but which I think are some important inputs, probably more proximal in your presentation.

The first has to do with the issues surrounding demonstration of asymptotically colonized individuals. In the data from Japan, as you noted, most of those appear to have been picked up by cultures done on contacts, some households, sometimes classrooms, business associated, whatever, where there has been an indexed case. They were not always stratified by either antecedent or subsequent illness.

In other words, some of these putatively asymptotically infected individuals may have had antecedent diarrhea and were simply convalescent excretors. Conversely, they may have been picked up in the incubation period. It is a fairly widespread practice within Japan to treat any person picked up with, quote, "asymptomatic colonization." And so I'm not sure we're going to be to dissect out which of those two possibilities occurred.

There is a paper that appeared this past year that looked at household contacts of children with HUS in the Netherlands, in which the predominance was O157-associated. There's a little bit of data in there, tantalizing, speaking somewhat again to the same issues. It does not tell you whether you just picked up a person who has previously had an illness. In the parents, there was a suggestion that that was true.

On another point, in terms of the genetic similarities, I think this is very, very problematic in terms of looking at EHEC, namely O157, and the EPEC

connection. While a number of genetic loci have been defined that are of great similarity, there has been more data that has been coming in recently suggesting that they may be organized differently or under different control.

A paper this past year showed that when you take the LEE out of EPEC and put it into a K12, you can confer the entire attaching and effacing phenotype. So it seemed to make sense, if you just did the same thing with the EHEC, or 0157, LEE, that it should occur. It did not.

Although the overall organization of the 0157 LEE crudely looks very, very similar to the EPEC one, the greatest degree of genetic variability is in the genes that control the interaction with the host. So kind of with these two pieces of information converging, I have a feeling--and it's only that, it's an intuition--that it may not be correct to be thinking about *S. dysenteriae* and EPEC as upper and lower bounds purely on the basis of their genetic complementation. It's possible that that, within the EHEC connotation, may place them outside of that range.

The last two are just very quick. The third point is--somebody help me here. I thought there was data on--a little bit on quantitation in the salami outbreak, West Coast salami outbreak. I cannot recall how much data was there for consumption, but I thought there was a little. Anne Marie McNamara and several other people in the room, I think, are on the paper from one of the food--it's not in the epi-oriented paper; it's in a second one.

MS. COLEMAN: Mark just reminded me we didn't have an attack rate for that outbreak. So we had a little food microdata, I believe, but perhaps not the case description.

DR. NEILL: Okay, because it is within that data that is the suggestion for some of the lowest possible exposures in terms of CFUs that have been demonstrated, to my knowledge, and I think Paul is indicating kind of the same.

Those are may major points. I have some other ones, but I'll communicate them to you later.

MS. COLEMAN: Thank you.

MS. OLIVER: John?

DR. KOBAYASHI: John Kobayashi, Washington State Health Department. With regard to the salami outbreak, that's my recollection that there was quantitation, but the number of cases was very small and may have been too small to generate attack rates.

At any rate, with regard to the 1993 outbreak, I think it may be that you know this already, but at least my recollection of the attack rate per number of hamburgers served in Washington State was about 1 per 1,000, which is more than that .00037, I think, that I saw there.

On the other hand, I think in one of your graphs I saw 1 per 1,000, so maybe you were correcting for Washington State versus outside of Washington State. The basic basis, I think, for that is ascertainment--especially at that time, ascertainment for *E. coli* 0157 cases in Washington State was a lot better than a number of the other states involved.

The other things are just a few tidbits with regard to the details of those burgers. My recollection is that they were one-tenth-pound burgers that were cooked in two minutes from the frozen state to a presumably cooked state. These burgers were cooked on an open grill without a weight above it, so that if there was buckling or bowing of

the hamburger that there might not have been adequate contact with the grill. These were marketed as children's burgers. They had a slightly heavier burger that was marketed for adults, so the bulk of the people exposed, I think, were children in that circumstance.

At any rate, the other thing is I believe that there were a number of temperature measurements that were taken during that time. As I'm saying that, I think you know that already with regard to the temperatures.

DR. POWELL: I just wanted to comment regarding the analysis that was shown here on the Pacific Northwest outbreak. This point that is shown on figure 39 is derived just from the Washington-based write-up, and rather than inferring or implying a degree of undercooking, this is the estimate of approximately 1 log without any cooking. And the most likely curve was derived, in part, from the venison jerky outbreak, and then our effort was then to use this as kind of a ground-truthing--on that curve, you see the venison jerky outbreak--and then just to see whether in the low-dose region it seemed to make any sense.

So, that is intended as a validation on the curve that is derived from the venison jerky outbreak, and we can impute from that a degree of undercooking which turns out to be somewhat less than 2 logs. Rather than making an assumption about the degree of undercooking, we can impute that to force that onto the most likely curve you would impute, I think it's about a 1.5-log reduction from the frozen state.

I also wanted to--I'm sorry--just make a clarification that the output from the preparation segment is for all ground beef servings consumed by all age groups, not just for those 16 and over, but that we have not distinguished the dose-response relationship for the different age groups. So all of the servings consumed by all age groups is output by the preparation segment.

MS. OLIVER: John, did you have any other questions?

DR. KOBAYASHI: No.

MS. OLIVER: Bill?

DR. SPERBER: Thank you. Bill Sperber, Cargill.

In discussing the 1993 hamburger outbreak, you pointed out the six MPN results and suggested that perhaps these weren't accurate and you didn't know if this was really a good way to estimate the infective dose. For these six numbers, the median count is about 2 per gram, and I would suggest that they should be treated as accurate estimates of an infectious dose because for this whole century we've had to use similar procedures for estimating infectious doses of other pathogens like *Listeria monocytogenes* and salmonella.

And at the very least, these methods, inaccurate as they may be, are showing us that some organisms like 0157 probably have a very low infectious dose, and other organisms like LM probably have a very high infectious dose. And until we have better methods that can more accurately identify CFUs, individual cells versus clumps, that sort of thing, we have to make the best use of these data, and I think it's legitimate to do that with these data.

MS. COLEMAN: Thank you. Yes, we really do intend to use them in a more formal dose reconstruction. But given that those are counts in a raw frozen product, somehow we have to get to what people eat, and so there are adjustments

that have to be made.

MS. OLIVER: Chuck?

DR. HAAS: Yes. First of all, Peg--

MS. OLIVER: Can you give your name again?

DR. HAAS: Chuck Haas.

I want to indicate that I find myself in, you know, pretty good agreement with what you've done, and so I think it's a nice approach. And I just wanted to add that our analysis of the animal 0157 data probably leads to a dose-response curve that is reasonably on top of what you've indicated as your median. We should compare those curves because I think it's going to be close to that.

MS. OLIVER: Paul?

DR. MEAD: Paul Mead. Just briefly to follow up on what Peggy said, I do think that while the salami outbreak, you cannot establish an attack rate because you don't know the number of people exposed, and so it perhaps doesn't give you the infectious dose, I do think it provides some of the really pretty good data in terms of the minimum infectious dose, in that I think there were on the order of seven or so samples tested, all of which were positive and contaminated at pretty low levels, and that there was fairly good consumption history at least for culture-confirmed cases.

Now, you don't know that that dose is the ID10 or the ID50 or the ID90, but it does give you a hint that somewhere on your curve it should come down to somewhere below 50 organisms, which that seems to support. And unlike the ground beef and those items, there's no additional cooking and factoring in that you have to worry about. So I think that paper--if there is some way to incorporate that data, it would be helpful.

MS. COLEMAN: Thanks.

MS. OLIVER: Are there any other questions and comments before we take a ten-minute break?

[No response.]

MS. OLIVER: Okay. Why don't we take a ten-minute break and then come back? Thank you.

[Recess.]

MS. OLIVER: We'll get started again. Mark Powell is going to give us a model summary and an epidemiological validation, and then we'll take some questions on that.

Mark?

DR. POWELL: Before moving to consider the epidemiologic data, I just want to try and recap very briefly.

Next slide.

Again, the scope of the risk assessment is limited to 0157 in ground beef.

Next.

For the production segments, our best estimate of the prevalence of 0157 in live cattle destined for ground beef production is 11 percent. The uncertainty range is on the order of 5 percent to 15 percent.

Next.

In the slaughter segment, our best estimate of the prevalence of positive combo bins is 23 percent, and the uncertainty there, depending on the class, ranges from 2 to 66 percent. Our best estimate of the concentration per gram in the combo bins is negative 4.5 logs.

And there's a lot of uncertainty regarding these

outputs. For example, for steer/heifer plants, the estimated relative frequency of containment in combo bins containing 1 log load of 0157 ranges from less than 10 percent to approximately 25 percent.

I'm recapping essentially what Eric and Wayne presented this morning.

For the preparation segment, our best estimate is that 81 percent of grinder loads contain at least 1 CFU, but again the loads tend to be very low and there's a great deal of uncertainty attendant to that estimate.

Our best estimate of the annual number of contaminated servings post-cooking is 375,000. That translates to a prevalence of about .002 percent, and again low levels, about 40 percent of the exposures in post-cooked servings being 1 organism, only about 10 percent of the exposures being doses of greater than 3 logs; a lot of uncertainty, again, attendant to those estimates.

We considered a number of alternative dose-response relationships, and these fall into two broad categories. The first category consists of models based on *Shigella* as a surrogate pathogen. Within this category, two model forms have been published in the literature, the beta-Poisson, the beta binomial. The second category is the envelope that uses the dose-response relationship for *Shigella* and EPECs as bounding estimates. Within this category, one alternative considers a variety of statistical dose-response model forms, and that was illustrated with the C-plus object that we ran during Peg's talk. And the other alternative developed uses the beta-Poisson curve and anchors the most likely value in outbreak in epidemiologic data.

So, that's a sum of where we've been. Next, I'll address the epidemiologic validation. In the presentation that I'll give you, I have deleted the second slide on the hand-outs. And the third slide, Epidemiologic Risk Factors, has been moved to the discussion of the proportion attributable to ground beef, which begins in your hand-outs on page 15. So those are the only changes that have been made. So I'll proceed then to get right into the analysis of the FoodNet data, page 4 of your hand-outs.

Our analysis begins with the reported population base rate in the five original FoodNet catchment areas during '96 to '98. These rates of illness per 100,000 person-years are then weighted by the population of the state in which the FoodNet catchment area occurs for the purposes of extrapolating to the national level. Thus, the rate reported in a large state like California is given greater weight than the rate in a small state like Minnesota.

Next.

To represent the annual variability in the number of reported cases, we placed the cluster-weighted rates from the three years of surveillance into a discreet, uniform distribution. And as we perform our simulation with each iteration of the model, the rates are drawn at random with equal probability from this distribution. And then to extrapolate to the national level, we simply multiply this distribution by the estimated U.S. population in '98.

Next.

These estimates need to be adjusted, however, for the recognized sources of underreporting because some ill

persons do not seek medical care, physicians do not obtain stool specimens from all patients, laboratories don't culture all stool samples for 0157, and at some proportion of labs the results are false negatives. With the exception of test sensitivity, each of these proportions is treated as dependent on whether the infected person presents a bloody or non-bloody diarrhea, so we first estimate the proportion of bloody and non-bloody cases.

We then characterize the uncertainty about the proportions of cases at each node in the pathway that leads to a successfully reported case. These proportions feed into a sequence of negative binomial distributions that are used to estimate the number of cases missed at each step. Then we sum the resultant two uncertainty distributions about the number of cases, both bloody and non-bloody, to estimate the total annual number of cases nationally. For the severe cases, defined as bloody diarrhea for which the person seeks medical care, we will subsequently estimate progression of illness to more severe health outcomes, such as hospitalization, HUS, or death.

Next.

We proceed by observing that 409 of 480 reported cases presented with bloody diarrhea. These data provide the parameters for a beta distribution that characterizes our uncertainty about this proportion that is centered about 85 percent. The data come from the first year of statewide surveillance in Washington, reported by Ostroff and colleagues, and the first year of FoodNet--that is, 1996--that was reported by Hedberg and colleagues.

Next.

In conjunction with the active surveillance system, FoodNet has conducted a number of companion surveys to estimate the degree of underreporting in the sentinel sites. Here, we observe the results of the FoodNet laboratory survey in which 79 percent of labs reported testing bloody stool samples for 0517, but only 47 percent of the labs reported testing all stool samples for 0157. These data feed into a beta distribution characterizing the uncertainty about the proportion of labs that cultured for 0157 in bloody and non-bloody stool specimens, respectively.

Next.

The sensitivity of the sorbitol McConkey agar, or SMAC test that is used by the labs to identify 0157 in stool samples is assumed to be 75 percent.

Next.

In a survey conducted in the FoodNet catchment area, 78 percent of responding physicians reported that they obtained stool specimens from patients presenting with bloody diarrhea, and 36 percent reported obtaining specimens from patients with non-bloody diarrhea. These data feed into yet another beta distribution characterizing the uncertainty about the proportion of the physicians that obtained specimens from patients presenting with bloody and non-bloody symptoms, respectively.

Next.

Regarding the proportion of ill seeking medical care, Cieslak and colleagues found that 55 percent of bloody diarrhea cases in an 0157 outbreak in Las Vegas reported seeking medical care. We used these data to characterize our uncertainty about the proportion of bloody cases seeking medical care. For the non-bloody cases, we used the results

of a FoodNet population survey in which 8 percent of the respondents who had had a recent bout of diarrhea reported seeking medical attention.

Next.

From this point, the negative binomial distribution is employed in a step-wise fashion to add to the reported number of cases those that are missed by the surveillance system due to test insensitivity, laboratories not culturing stool samples for 0157, physicians not obtaining stool samples from patients, and ill persons not seeking medical care.

The highlighted figures in this table represent the expected value of the annual number of severe cases, approximately 7,500, and the total annual number of bloody and non-bloody cases. Taken together, the expected value of all cases is approximately 73,000, and in just a moment I'll present the uncertainty that is attendant to this estimate.

Next.

Proceeding from the estimated number of severe cases, we characterized the uncertainty regarding the proportion of such cases that progressed to more severe health outcomes--hospitalization, HUS or TTP, and death. These uncertainty distributions are based on CDC data on disaggregated health outcomes from 203 outbreaks reported during 1982 to '98. I would note that applying these attack rates to all cases involves an assumption that the severity of outbreak in sporadic 0157 strains is similar.

Next.

We then generate the estimated total number of cases of 0157 using Monte Carlo simulation methods. As you can see, there is considerable uncertainty in these estimates.

Next.

We proceed by characterizing our uncertainty regarding the etiologic fraction of 0157 cases due to ground beef. During 1994 to '98, ground beef was identified as the likely vehicle of infection in 31 percent of reported outbreaks where a likely vehicle of infection was identified. Eighteen percent of these outbreaks were attributed to ground beef. These limited data do not provide a precise estimate of the proportion of total 0157 illnesses--I'm sorry--18 percent of the illnesses in the outbreaks were attributed to ground beef.

These limited data do not provide a precise estimate of the proportion of total 0157 illnesses due to ground beef consumption. And, in general, we are wary of relying too heavily on outbreak information to characterize the proportion of cases attributed to ground beef. But the outbreak data do help bound our uncertainty about this etiologic fraction.

Next.

While ground beef is the most frequently identified source of outbreaks, most cases of 0157 are estimated to be sporadic. In the first nationwide case control study of 0157 conducted in '90 to '92 by Slutsker and colleagues, consumption of pink ground beef was the only dietary risk factor independently associated with diarrhea in multivariate analysis. The population attributable risk for this behavior at that time was 34 percent.

More recently, Kassenborg and colleagues also found that consumption of pink ground beef was a

statistically significant risk factor in a case control study conducted at five FoodNet sites during '96 to '97. A preliminary multivariate estimate of the population attributable risk from consuming pink hamburger or ground beef was 19 percent. We used the most recent case control findings to anchor our uncertainty about the etiologic fraction of cases due to ground beef.

Next.

An estimate derived just on the basis of the outbreak-associated illnesses due to ground beef is consistent with case control findings, but it seems to us over-confident. An estimate derived from the proportion of outbreaks due to ground beef is less confident but seems biased in light of the case control findings.

Therefore, we characterize our uncertainty about the etiologic fraction as a pert distribution with a minimum equal to the 2.5th percentile of distribution A, based on the outbreak illnesses, a most likely value equal to the median of distribution A, and the maximum equal to the 97.5th percentile of distribution B, which is derived from the occurrence of outbreaks. The expected value of this pert distribution is 21 percent, approximately.

Next.

This figure presents the three different sources of information that could be used to depict the uncertainty regarding the proportion of illnesses due to ground beef. The tight green distribution is the one that we felt was over-confident, derived from the proportion of outbreak-associated illnesses due to ground beef, and it's centered about 18 percent.

The broad black curve, which we felt was less over-confident but perhaps biased, is derived from the proportion of outbreaks due to ground beef. It's centered around 32 percent. The intermediate brown distribution is the pert distribution that we've defined and used to characterize the uncertain proportion of illnesses due to ground beef. Again, it's anchored with the case control data and bounded by the outbreak data.

Next.

To estimate the number of cases of 0157 due to ground beef, the estimated total national annual number of cases of 0157 is multiplied by the preceding pert distribution. The resultant distribution of the total number of cases of 0157 due to ground beef has a median of approximately 16,000, and a 95-percent confidence interval of approximately 9,500 to 29,000. Approximately 10 percent of the cases meet the severe case definition. The estimated annual number of deaths due to 0157 in ground beef ranges from 5 to 20.

Next.

So, again, this is showing the curve that Peg presented earlier. This figure compares the epidemiologic estimate, which is the furthest to the right--this is the epidemiologic estimate of the number of cases of 0157 due to ground beef--and the results predicted by three of the dose-response models discussed during Peg's presentation.

Here, we have integrated the dose-response models over the most likely exposure distribution that is outputted by the preparation segment. We have not yet pushed through the bounds of the preparation segment, so the full uncertainty in the three model curves, which are those to

the right, is not fully reflected. But this gives us some means of relative comparison of the three dose-response alternatives.

All of the models pictured here overlap to some extent with the epidemiologic estimate, but the extent of the overlap is greatest for the beta-Poisson envelope. Now, this is not particularly surprising, since the most likely value for this dose-response model has been anchored by the epidemiologic estimate. So it, in a sense, has been given an advantage over the other models which do not use the epidemiologic data. Those are set aside independently for validation. Nevertheless, even with the beta-Poisson envelope that is anchored, the overlap is not complete because the upper and lower bounds of the envelope are independent of the epidemiologic estimate.

Next.

This figure presents in descending order the rank correlations of various factors in the model for the total number of cases of 0157 due to ground beef. The pattern that emerges is that if we seek to reduce our uncertainty in the overall number of cases, then we should focus on enhancing the data on the non-bloody cases, beginning with those that don't seek medical care.

Toward the other end of the range, it seems that if we seek to have a more precise estimate of the overall number of cases, then we may gain relatively little from decreasing our uncertainty about the proportion of 0157 cases that are bloody. As is often the case, however, the results of the sensitivity analysis depend on what question you're trying to answer.

Next, and this is my final one.

If, rather than trying to reduce the uncertainty associated with the estimated total number of cases due to ground beef, you are instead seeking to reduce the uncertainty in the estimated number of deaths due to 0157 from all sources, then the pattern that emerges from the sensitivity analysis is that you're keenly interested in improving your state of knowledge about the disposition of the bloody cases than about the overall rate of 0157 in the population. And these results help to underscore the importance of knowing what question you're trying to answer in any sort of analysis.

And that will be the end. Now, are there any questions specific to the epidemiologic validation or our efforts to correlate the model outputs with the epidemiologic estimate?

MS. OLIVER: Do the Committee or the experts have any questions or comments?

John?

DR. KOBAYASHI: John Kobayashi, Washington State. Not a question, but a comment. There was an old study authored by McDonald and O'Leary in JAMA in 1986, I think it was.

DR. POWELL: Eight per 100,000?

DR. KOBAYASHI: Right. At any rate, I'm not sure if it adds much to Cieslak's case control study, national case control study, but I just wanted to make sure you're aware of that. And I think an advantage of the study we did back in the '80s was that it was a very defined population with an HMO, with a very clear population base.

Basically, all of the individuals who sought

medical care and had a stool culture were tested for 0157 at that time for one year. And an association was found with hamburger, so you can get an estimate of the burden of illness in the absence of outbreaks for a one-year period.

DR. POWELL: Right. Originally, we had used that as a bounding estimate, and used the raw FoodNet data as our lower bound, using the McDonald report as the upper bound. But we were, I think, convinced that it would be more appropriate to use the approach that CDC has used and take the active surveillance data that is more current and then apply these uncertain proportions in this step-wise fashion for underreporting to arrive at a bounding estimate, given that uncertainty about the active surveillance data. The bottom line was that our results didn't change a whole lot from what had been used prior to that with using the McDonald study as our upper bound estimate.

DR. HULEBAK: This is Karen Hulebak. Mark, could we go back to the third to the last slide, Comparison of Epi Estimates with Other Model Predictions, and talk a little bit more about what you're showing there--

DR. POWELL: Sure.

DR. HULEBAK: --the epi data being the curve farthest to the left, and then our best model prediction?

DR. POWELL: Right. Well, I guess I'm hesitant to say that we have a clear winner. I think it's obvious--well, let me get into answering your question. This blue distribution is the epi-based estimate that's--

DR. HULEBAK: It's a little hard to see color.

DR. POWELL: Oh, okay. Yes, that was--which is furthest to the left; I guess that was my right, your left, distribution. I apologize. Your other left, your other left--distribution is the epi estimate, derived totally independently from the model, okay.

This broad distribution of the number of cases, okay, is that which was developed by Harry Marks and is based just on Shigella. And we insert this as kind of a place-holder for all of the models that have been developed and published in the literature based on Shigella as a surrogate for 0157, suggesting that using Shigella as a surrogate--

DR. HULEBAK: Doesn't really match up very well.

DR. POWELL: --may overstate the cases, although given the level of uncertainty about that data, there is still some overlap, although, you know, not a terrible lot.

This curve is that which was developed by Clark Carrington. These two are envelope methods using Shigella as the upper bound and EPECs as the lower bound, and this curve was not anchored to the epidemiologic data or deriving a most likely value utilizing our best estimates of the exposure distribution.

I would also add there isn't a whole lot of overlap with the epi distribution, but this particular implementation of the object that has been developed by FDA reflects only model uncertainty and not within-model uncertainty. So that distribution one would expect to be somewhat more broader. When we run that again, there would be a little bit more overlap, but still the central tendency is, you know, somewhat high for that curve, okay.

Now, it's true that the beta-Poisson envelope has the most overlap with the observed data, okay. But one of the questions that we pose to the Committee is, you know, is

it, you know, legitimate to utilize this curve which has been anchored, okay, as opposed to these which take a more neutral or uninformed sort of an approach, at least for specifying the most likely value within the envelope.

Now, I would say that again I'd just repeat that the only value that was anchored in the beta-Poisson envelope is the most likely value within the bounds, okay. That was derived from initial estimates of our uncertainty about the venison jerky outbreak, okay, and then using concepts that are sort of maximum likelihood estimation concepts saying what beta-Poisson parameters, given the best estimate of the exposure output and our best estimate of the occurrences, the epidemiologic data, would be most likely to be observed under those conditions. So that's the anchoring that took place with the beta-Poisson envelope.

DR. HULEBAK: And the beta-Poisson envelope is our own prediction. I mean, it's--

DR. POWELL: That was one of two that was developed by the team.

DR. HULEBAK: Right, right.

DR. POWELL: So we have an unanchored envelope and an anchored envelope.

MS. OLIVER: Paul?

DR. MEAD: Paul Mead, CDC. I have to confess--I'm not sure if it's late in the day or something in those cookies, but my head is kind of spinning at this point.

DR. ROBACH: Mine, too.

DR. MEAD: A couple of quick questions, and I'm not sure how it influences--or comments--I'm not sure how it would really work out in this model, but to the extent that you use the outbreak data, I think it might be appropriate to not include outbreaks due to unknown etiology.

DR. POWELL: We have.

DR. MEAD: Okay, to only use those where the etiology is known because otherwise--I don't know that that makes a major difference.

DR. POWELL: Yes.

DR. HULEBAK: But we've done that.

DR. MEAD: Okay. On this table, the unknowns are in here, so I thought perhaps that influences those percentages. The percentages given in the table, you'll see under 1, 25 percent of outbreaks are due to--

DR. POWELL: That's number 2 in your figure? Yes, that was deleted from the presentation and that was initially intended to serve as a means of kind of background, laying out, and is not incorporated in the analysis. It's only based on outbreaks. I think it's slide 13. That was the information that was used in just number 13, and there we've limited--actually, I think about 40-some outbreaks with unknown etiology occurred between '94 and '98, and those were omitted from that data set.

DR. MEAD: Okay, great, thanks. The other question, I guess, is if I understand this, your results are very much linked to sort of the attributable risk associated with the consumption of pink hamburger. And I guess this opens up the broader question and it kind of gets back to one of the earlier talks about cross-contamination and its rule.

I mean, in one investigation we did of sporadic illness we didn't find any association, or consequently any attributable risk with eating undercooked hamburgers, eating

pink hamburgers. We did, however, find an association with not washing your hands after handling those. Now, I guess that gets into some sort of philosophic issues about what's the error there. Is it hand-washing or is it the fact that it was in the hamburger in the first place?

But I'm concerned that the sort of attributable risk to pink hamburgers, although it has been statistically significant in some settings, really underestimates the role of ground beef in terms of bringing this into the household, and even in undercooked hamburgers which may or may not be pink.

DR. POWELL: It may be, and this is why we would feel that simply utilizing the confidence interval around that population, attributable risk from the case control study, would probably understate our uncertainty about that. And that's one of the reasons we've tried to use kind of bounding estimates that utilize other information to characterize the proportion, you know, that etiologic fraction.

Certainly, some proportion of the outbreaks that are identified as, you know, a non-meat source or something else--the origins of that infection were ground beef, and

that's an uncertain proportion. But I think what we tried to do was not hypothesize, but treat the data that we have in a way as to try and acknowledge the uncertainty that is attendant with it and not just rely on the confidence interval about the case control results.

MS. OLIVER: Paul, did you have any other?

DR. MEAD: No. Thank you.

MS. OLIVER: John?

DR. KOBAYASHI: A couple of comments.

MS. OLIVER: Can you identify yourself?

DR. KOBAYASHI: John Kobayashi, Washington State Health Department. A couple of comments. You may know this, but in recent years, I think, since the beginning of '98 in the international classification of disease coding for hospital discharge data and deaths, there has been a code for hemolytic uremic syndrome that wasn't present previously.

While that's not a lot of time, maybe if you look at national data, you could get an idea as to the burden of HUS, of which I think in the United States is almost all E. coli. At least that will give you some information about the total burden of E. coli, not necessarily that related to hamburger.

The other comment, sort of following on Paul's issue of secondary cases, it's worth remembering in the '93 outbreak that two of the three deaths that occurred were secondary cases. And it may be worth it to factor in some sort of occurrence of secondary cases, such as looking at the proportion of secondary cases in that outbreak. In that particular outbreak, we made a lot of efforts to reduce secondary transmission, and I doubt that those kind of efforts are done in response to sporadic cases. So that might be a conservative estimate of how much secondary spread occurs related to contaminated hamburger and 0157.

DR. POWELL: Well, your point is well taken. I would presume that some unknown proportion of the cases in outbreaks where the likely vehicle of infection is identified as ground beef are secondary cases, and so to

some extent that's built into the outbreak data.

Am I mistaken?

DR. KOBAYASHI: I'm not sure.

DR. POWELL: The number of cases are not partitioned out this many from an outbreak where the likely vehicle of infection was ground beef. We'll put these in the secondary transmission, then we'll put these in the ground beef bin. My understanding is that--

DR. KOBAYASHI: They are all included.

DR. POWELL: So you've already got some of that in the outbreak estimates.

DR. KOBAYASHI: Maybe so.

DR. POWELL: So that proportion is the observed proportion.

DR. KOBAYASHI: Right.

DR. POWELL: If you do have some data that would help us estimate the proportion of secondary cases from the primary cases, that would be very helpful.

DR. KOBAYASHI: Yes. I think your point is well taken that at least in our write-up in the '93 outbreak we did include both secondary and primary cases.

DR. POWELL: Sure, sure.

MS. OLIVER: Does anyone else have any questions or comments for Mark on the model summary and epidemiological validation?

[No response.]

MS. OLIVER: If not, why don't we move into the next section, Mark?

DR. POWELL: Great, so I'll ask the panel members to all come up to the table now. And at this point, we'd like to return to the initial points simply as a point of departure for a broader discussion. Again, we don't want to limit the discussion to these questions, but we felt that it would be helpful for us to pose some questions as a way of initiating some discussion.

So the first set of questions--if we have time, I think we could return to this resolution question, since I'm sure some people are going to be heading for the airport soon. Let's deal with the second of these.

Is the panel aware of any evidence that would help us to, or permit us to adjust for the specificity of the microbial analysis? There's been a lot of questions about the test sensitivity, and a lot of our effort was devoted to coming up with means of adjusting the apparent prevalence of surveillance and other data for test sensitivity, both in terms of the sample size, the microbial methods that were used, and making it also in some cases conditional upon the concentration on the incoming product.

But specificity is an issue that we've not made any adjustments for, and so we would ask if the panel is aware of any evidence that would enable us to make that adjustment.

MS. OLIVER: Does anyone on the panel have any information, any comments on what he's asking?

DR. POWELL: The methods would be very similar to what we had done for sensitivity. So it's not a methodological limitation, it's a data limitation.

MS. OLIVER: Art?

DR. LIANG: Art Liang, CDC. I don't have an answer. I have another question, and that is I think I've heard the term "sensitivity" used in two different ways.

You know, I'm used to thinking of sensitivity as, you know, not as a positive predictive value, which is, I think, the other use of sensitivity that I've heard earlier in the day. I don't know how you used it.

DR. POWELL: Eric?

DR. EBEL: Well, I think we just want to define specificity in this case primarily as the probability of false positive results. I'm sorry. That would be one minus the probability of two positive results, but we're interested in trying to understand if any of the positive results that we're getting are, in fact, false.

Obviously, there's a whole series of explanations for why you might get a false positive sample. We haven't accounted for that in our analysis. We don't know that it's an important issue, but if the Committee feels that we should adjust for that, we'd like to know that.

MR. SEWARD: This is Skip Seward, with McDonald's. We talked a little bit before about this, but I don't think it's a very large issue that deserves much additional attention as long as when you get the information, in the methods it's clear that the people have taken the identification all the way out to the very endpoint and not relied on some previous endpoint prior to full elucidation of what the microorganism is to say that they have a positive.

A lot of times, in industry, for example, they will only go part way and just stop the test. And in some data, that may be reported as a presumptive positive which eventually gets lumped into some estimate of a number of positives. So I think that's the only risk involved in that, but if you go all the way, I would say it's not an issue worth adding to your deliberation.

MS. OLIVER: John?

DR. KOBAYASHI: John Kobayashi. I don't have any advice for you with regard to this question, but I wanted to mention that among the CDC and state health departments there's a significant amount of discussion with one of the major national laboratories which does testing on clinical specimens. And apparently there are plans for this national laboratory to stop testing for E. coli 0157 and they would simply rely on the SLT test.

And although they are apparently willing to send isolates and what not to state laboratories for further identification, this may significantly affect sensitivity and specificity of measuring the burden of E. coli 0157 in the long run.

MS. OLIVER: Any other comments on this question?
[No response.]

DR. POWELL: Next, then, we'll proceed to the production segment. We would glad entertain the Committee's recommendations if they can think of a better way than what we have presented to link live cattle to contaminated carcasses. We're aware of the limitations of the data that were currently used to quantify that link, but are unaware of a better way to establish that link. And a related question is are there data or methods currently available that would improve the quantitative links among fecal, hide and carcass contamination.

MS. OLIVER: Dale?

DR. HANCOCK: Dale Hancock, Washington State. I think that the amount of data here is really limited. That

one study--

DR. POWELL: Chapman?

DR. HANCOCK: --Dr. Chapman's study, and that's a tiny little study. And so, you know, the obvious answer is a U.S. study with lots of animals, but I guess a less obvious answer is it would be better to tied at the group level, it seems to me, because at least from available data it is really clustered at the pen level, so that our high prevalence pens--do they have high prevalence carcasses, and what's the function going on there at the group level?

And then I guess the nice thing would be to extend that to the ground beef level, although I don't have any--or at least the boxed beef or the combo level, although that might be super hard to do.

DR. POWELL: Are you aware of any efforts to gather that sort of data that would take into consideration the group-level effect?

DR. HANCOCK: Yes. I hear MARC, the Meat Animal Research Center, has done something on that, but I don't really know. They kind of play their cards a little close.

MS. OLIVER: Isabel?

DR. WALLS: I'd like to see more data on contamination of the hide. You know, maybe a study could be set up, and I would also like them to consider seasonality, if they could.

MS. OLIVER: John?

DR. KOBAYASHI: John Kobayashi, Washington State Health Department. Of course, I'm not a food scientist, a modeler, or a member of the beef industry, and I think my comment needs to be taken with a grain of salt. But at least my two cents' worth is I don't understand why it's not possible when cattle are slaughtered to tie on a sheaf of bar codes onto that carcass, and as that carcass gets separated from the hide and dismembered and what not various bar codes accompany those products along the production line, because it seems to me that there are many, many questions as to relationships and probabilities that are pretty uncertain at this time. And I think that those could be resolved with, you know, more detailed tracing of products and seeing where contamination goes.

MS. OLIVER: Thank you. Does anyone else have comments on this question?

[No response.]

DR. POWELL: Moving then to--

DR. POWELL: Dane?

DR. BERNARD: I'm sorry for the delay. Mine is actually a question--Dane Bernard--for you all.

MS. OLIVER: Can you identify yourself? Oh, I'm sorry.

DR. BERNARD: I did.

MS. OLIVER: I know. I apologize.

DR. BERNARD: Have you asked for studies that address your second question there? If so, obviously there are many techniques available to us today to mark organisms that could be included in a feeding regimen, for example, in feedlot that you could then track their eventual translocation to a finished carcass.

And to address John's intervention regarding tagging, I'm sure that the experience here has been the same that I have had when this subject comes up because it goes in so many different directions when a carcass doesn't go

into one type of thing. It goes into sausage. Parts go to sausage, parts go to this, parts go to that. It just goes phht.

DR. POWELL: Was that the technical term for--

DR. BERNARD: Yes.

DR. POWELL: Yes.

[Laughter.]

DR. BERNARD: At least at NFPA, it is. We have a definition on my wall. So it's tough. It's very expensive to do that.

But back to the central question, there are techniques, and I think it would be interesting to do that kind of study. But I don't know whether you have asked for that or whether you need a recommendation from here, but I agree with Isabel's earlier intervention that it would be nice to have some of that work not only to look at hide, but to start out with fed cattle or a marked strain and then follow where that might lead to and in what quantities.

DR. POWELL: The only answer on the part of the team would be that part of our effort through the Federal Register, you know, notice and comment procedure and the public meeting that was held in October '98 was that we requested that all relevant data be submitted to the docket.

MS. OLIVER: Mike?

MR. ROBACH: Mike Robach. Has there been a request for a sister USDA group such as ARS to look at the ecology of this organism as it relates to cattle production and cattle slaughter, something similar to something we've just completed in the poultry industry looking at the ecology and modes of transmission in reservoirs of campelobacter, both in live production and following those flocks through the processing plant?

It seems to me that we generated a tremendous amount of valuable information from hatcheries, from feed mills, from grow-out facilities into processing plants that have allowed us to begin targeting intervention strategies to reduce the incidence of campy in poultry. And it seems to me that this was a good combination of government-focused research at a problem with strong industry cooperation.

Has anybody approached that thought with ARS?

DR. POWELL: Well, my only piece of information that I would add is that I know that in the CSREES extramural grant solicitations in the last couple of years, that sort of information, or those sorts of proposals have been invited through the RFP process. And that is really, you know, a large chunk of money relative to the intramural research monies. I'm unaware of what sort of success rate there have been for proposals to look at those issues.

MS. OLIVER: Dale?

DR. HANCOCK: Yes, just to address Dr. Kobayashi's point--

MS. OLIVER: Can you identify yourself for the record? I'm sorry.

DR. HANCOCK: What did you say?

MS. OLIVER: Can you identify yourself for the--

DR. HANCOCK: Dale Hancock, Washington State.

MS. OLIVER: Can you speak in the microphone, also?

DR. HANCOCK: To address the issue of animal identification, while I agree that's a great idea and we should do that at some point, it's not required to answer

this question. All we need for this question is cooperating feedlots, which are no problem; cooperating slaughter plants, which are a little bit more of a problem; and then cooperating government agencies agree not to use surveillance data for regulatory purposes, which admittedly is a little bit of a problem. So it should not be that overwhelming to collect data to answer these questions, it seems to me. And with regard to the point about the ecological studies, there are a number of groups that have studies underway at the farm level, although we can always use more.

MS. OLIVER: Colin?

DR. GILL: Some of my colleagues have a scheme afoot to follow generic E. coli contamination through the packing plant using molecular techniques of strain differentiation. They assure me it can be done and I have to believe them. As far as cattle identification is concerned, there's a whole industry concerned with carcass identification which is moving ahead quite rapidly, I believe.

MS. OLIVER: Jim?

DR. ANDERS: Jim Anders, North Dakota Health Department. I did ask a question this morning. I still feel that the hide and the carcass contamination--any numbers that we currently have on those have been with methods that may not be standardized methods. And so down the line I guess I agree that we need studies on those.

And when we get to the carcass contamination, we have to be very careful because, as I mentioned this morning, some of those studies may be done on very small numbers of grams and very small numbers of numbers and may not be reliable, which seems to me that would make a difference in the dose-response.

DR. POWELL: It certainly would, and again we've incorporated not only the microbial test sensitivity and what we know about that in the adjustment from apparent to true prevalence, but incorporated in that uncertainty is also the size of the sample, okay, and the concentration because obviously at a lower concentration any given test method is going to--at a lower concentration, it will be less likely to detect the organism. And so those sorts of considerations have been factored in, and we'll try and make that more clear, I think, about how we've gone about that.

MS. OLIVER: Any other comments on this question?

[No response.]

MS. OLIVER: I don't see any.

DR. POWELL: So moving on the slaughter segment, we would ask what sort of evidence would the Committee feel might be necessary to satisfactory quantify the link between hide and carcass contamination. We're not aware of any such data, but we would invite your comments as to what sort of data would be adequate.

MS. OLIVER: Does anyone on the Committee or any of the experts have any comments, thoughts on this?

Dale?

DR. HANCOCK: This is Dale Hancock from Washington State University. Here again, I think the group-level data becomes quite important to look at prevalence on hides and in carcasses at the group level, and the same sort of study that looked at fecal prevalence versus carcass prevalence could look at this. And actually I think there is a study

that is addressing this issue to some degree going on at MARC.

DR. POWELL: At the group level?

DR. HANCOCK: That's what I understood, but that's not real authoritative.

DR. POWELL: So if I interpret your comment correctly, a study that would simply be a random study, say 1 in 100, 1 in 300, 1 in 500, would not be able to get at an important factor that would affect that relationship?

DR. HANCOCK: It would not get at it from the standpoint that these things vary at a group level. I mean, at least that's what the data suggests, so far as there are groups with high prevalence. And presumably their high prevalence is much higher because it represents maybe several weeks' contamination. And so to my way of thinking, that would be much better done at the group level.

You could look at individuals within groups to see if it made any difference whether that animal was positive on its hide versus its carcass. But then are groups with a lot of hide contamination--are they more likely to have a contaminated carcass, and what's the function that describes that relation?

MS. OLIVER: Art?

DR. LIANG: Art Liang, CDC. I just have more questions. I'm sure this is a stupid question, but I thought one of the wonderful things about models is that you didn't need any data and that you--

[Laughter.]

DR. LIANG: So why is there a concern about this particular step versus other places where you simplified the model? Maybe you've done some sensitivity analysis and this turns out to be a critical node, and so maybe that's the answer. I don't know.

DR. ROBERTS: Well, actually, you're right.

MS. OLIVER: Can you identify yourself, please, for the record?

DR. ROBERTS: Tanya Roberts. Clare Scott and I did another paper where we looked at some of the procedures. We didn't include fabrication, which Colin Gill suggests could be very critically important. But when we looked at dehiding, chilling, evisceration, and decontamination in a hot water wash or steam pasteurizer, the dehiding was by far and away the most significant factor.

Now, this is a very simple model that we kind of abstracted out here. We took, you know, good, improved versus not quite so good levels that you might expect in two different kinds of systems based on rather limited data we could find and ran it through the model. So I don't want to say that this is the last word here, but it's suggestive that that would be a very important place to collect more data.

DR. POWELL: Mark Powell. As Dr. Gill suggested, it's kind of a prime facie case of an important data gap because it's a small study and it's not national. It's not U.S.-based, but it's the only one.

MS. OLIVER: Jim, did you have any other questions?

DR. ANDERS: Oh, I'm sorry. Let me put that down.

MS. OLIVER: Mike?

DR. ROBACH: Mike Robach. I think the answer to some of these questions--you know, what evidence would be

necessary--I think simply you need more evidence. And I think you're absolutely right; what you have are very small numbers and maybe not indicative of what happens in this country. We also have to understand that we've got two different systems, one that is taking care of feedlot animals and the other one that is taking care of culled animals. And I think you've clearly identified differences in those two rearing systems.

And so there simply has to be more information generated under the conditions in which we're currently operating to base this very important node on. And I agree with you, I think it is an extremely important node, and a lot of assumptions made here, you know, drastically impact the numbers that you're seeing at the end of the model. So this is extremely critical, in my opinion.

DR. POWELL: Mark Powell. Well, I guess my response would be that more information would reduce our uncertainty. Our uncertainty about the model predictions was shown by those error bars that essentially, you know, reached from one end of the scale to the other--

DR. ROBACH: Right.

DR. POWELL: --are considerable. And so I have, you know, greater confidence that it would tighten our estimates. I think arguably the results of the baseline model are reasonably consistent with the epidemiologic evidence, at least within an order of magnitude, which for models is pretty close to dead-on. And so I think that the additional information would be extremely helpful in tightening our uncertainty and being able to focus, you know, on where the key points in the process might be.

I think Eric has another comment.

DR. EBEL: No. I was pushing my microphone away.

[Laughter.]

DR. POWELL: I think Eric will hold his powder dry.

MS. OLIVER: Any other comments on that point?
Colin?

DR. GILL: Just one thing. Could I just ask--

MS. OLIVER: Can you identify yourself again?

DR. GILL: Colin Gill. These links between hide and carcass contamination--do you consider evidence from generic E. coli equivalent to evidence of potential contamination with 0157, or do you actually want data on 0157, because data on 0157 is just about impossible to collect because there's not enough of it? So we can get strings of zeroes anytime, but how do you view the data on generic E. coli?

DR. ROBERTS: Tanya Roberts. In an earlier version of the model, I actually did use generic E. coli, and we adjusted it down, though, by 1 log based on the Zow and Doyle study looking at fecal shedding, in that the 0157 were 1 log less. But that tended to give counts that were--that was based on Graham Bell's work, where he was taking a piece of the hide and putting it upside down on an agar plate to mimic what happened if the hide would slap back on the carcass.

And the counts tended to be 1 log too hide based on the FSIS data. So it suggests that maybe we either--we need to make sure that the aerosol contamination is included, too. So maybe we just don't want to look at hide slaps; we want to look at the transfer from gloves, which

may be less, and the aerosol contamination. And so there's maybe a lot of adjustment factors we might have to take into account for the generic E. coli.

If the ARS data says that it's very high in some herds in summer months and early fall months and you're getting, you know, 25, up to 50 percent of the animals in a herd going to a slaughterhouse infected, then maybe it's not such a rare event in those seasonal things. And maybe if you could collect the 0157 data in the right season, you

could find a good relationship between a contaminated animal with its hide and its feces and what happens to the carcass level.

DR. GILL: So if I understand, you do want 0157, not generic?

DR. ROBERTS: Well, we would prefer that. I don't know how to--maybe Eric and Wayne have some insight on this, too, or Mark.

DR. EBEL: This is Eric Ebel. Yes, we do want 0157 data. I guess the one concern--well, one of the concerns with generic E. coli data would be the ubiquitous nature of, you know, E. coli in or on cattle come into slaughter. And then trying to develop a correlation with the prevalence and concentration on carcasses would just be a more difficult correlation to demonstrate because of the fact that, you know, we might have 100 percent contamination in the live animal. Then anything else on the carcass makes the correlation a little less defensible, whereas with something that's less common than 100 percent in the live animal status would allow us to have pretty good comfort level in the correlation we can develop for 0157.

DR. POWELL: And I would add that it's probably--Mark Powell--presumably, it has to do with the levels as well, not only that about 100 percent would be positive for generic E. coli, but presumably the levels, given that it's positive for generic E. coli, would be positive, and that could affect the link in terms of prevalence.

Now, for generic E. coli, as Tanya was suggesting, we have used generic E. coli information in terms of the direction and the magnitude of changes once 0157 is on the carcass, okay, making the presumption that, say, a treatment that reduced generic E. coli, a physical treatment that reduced generic E. coli by one log would also reduce 0157 by 1 log. So we would invite more generic E. coli data and have used it, but not for the link between the status of the live animal and the prevalence of contaminated carcasses.

MS. OLIVER: There were a couple of others with comments. Dane, do you want to do a quick one, and then John, and then we could move on to the next question.

DR. BERNARD: Yes, thank you. Dane Bernard. Very quickly, 0157, yes, and I would agree with Dr. Gill's previous intervention about if you want to look at where we get contamination, you can look at further processing seems to be a good source. But the central question is where does the 0157 come from, and that does not, according to the correlation studies that we've seen--and I recall the one by Acuff, et al, where they didn't find any statistical correlation between occurrence of anything and 0157. So we don't have an effective marker.

Further, there was an intervention much earlier in the meeting that I'd just like to bring up once again, and

that has to do with outbreaks and how they are--we have clustered cases. Your output from what you've done is a distribution over the entire population of outputs of 0157 in ground beef. But recall that most of our problems seem to be centered around outbreaks, even sporadic cases.

We're getting better at linking those together and saying that they had a common source. And I think that as you go forward, maybe you should consider that unique event because what you're looking at is what happens normally. That's my impression of what you've got here and the distributions that happen normally, whereas there may be an event, a catastrophic event, a punctured gut, a dung ball, a hide slap has been brought up, that then carries through the system and results in your outbreak.

So there are a couple of scenarios here and I think as you go forward, you may have to consider that. I don't know how you do that, but I'd just like to get that on the table for further thinking.

MS. OLIVER: John, did you have a quick comment?

DR. KOBAYASHI: John Kobayashi, Washington State Health Department. Just a quick comment. In investigating hospital infections, like in surgical suites and what not, it's not uncommon to spray an ultraviolet dye or something like that on the field or some other area, do a mock operation, and then see who glows at the end of this procedure.

And one would think that that would be an easy way to gather some data on contamination of the carcass from the hide and, you know, spray some hides and various parts of the anatomy and all that sort of stuff, and then see where the carcasses glow in various situations.

MS. OLIVER: Did you want to move on to the next question?

DR. POWELL: Yes, we'll move on to the next question. I'm sorry. Eric wanted to make a final comment.

DR. EBEL: I don't know if it's a final comment. This is Eric Ebel. I just wanted to mention that another source or data is salmonella sampling data. And we have looked at some of that and it's kind of surprising, but at a very crude level we found similar--at least at the level we're analyzing things, about 30 percent of animals coming in at least intestinally colonized with salmonella came out. And that was actually done at the group level. There was about a 30-percent correspondence, then, with contaminated carcasses.

One of the problems with hide sampling and with carcass sampling is the methods of doing those samplings, and better understanding of how sensitive those methods are, how many are we missing, is needed before we get too fired up about doing a lot more of the sampling. So I think targeted research in that area of, you know, how confident can we be and the results of standardized carcass and hide sampling will be useful.

DR. POWELL: Okay, I'd like to move on then to the second question that we'd like to pose regarding the slaughter segment, and that is that we've attempted to develop a mechanistic model that follows product through the slaughter plant, in large part due to our efforts to satisfy one of the objectives, which is to try and identify potential critical control points in the farm-to-table continuum.

But we don't have anchors everywhere, obviously, real data. And so we ask would it be preferable to develop a strictly data-anchored model which doesn't attempt to model processes between the monitoring points, and if so, what data would be required to develop this sort of an empirical model rather than one that is more predictive.

MS. OLIVER: Does anyone have comments on that? Chuck?

DR. HAAS: Chuck Haas. Well, as somebody who is more of a modeler and less of a food person, I guess my bias is mechanistic models are preferable, in that if your overall objective presumably is to look at possible regulatory scenarios or interventions and if you go strictly the data-anchored route, that simply describes the state of practice at present and gives you no ability to estimate what would happen.

MS. OLIVER: Dane?

DR. BERNARD: Dane Bernard. As a non-modeler, I agree with the modeler. I think if your ultimate purpose is to go back and develop some interventions, then that's what you have to do. There was one element in that discussion, though, that came up that I'd like to bring up again, and that's the modeling in the cooler.

I think Dr. Gill made an intervention that was very important. He has done some carcass mapping; others have done carcass mapping. You made an assumption of general distribution over the carcass that I think is not supportable by what we know about localization of bugs on the carcasses. Head meats, cheek meats are very highly contaminated. Based on the way carcasses are slaughtered, I think you need to consider where they would be and how the chilling is delivered first to the surface, which is where they are likely to be, and how that might affect the growth of your model.

Thank you.

DR. POWELL: Mark Powell. If you're aware of any enumeration data on head and cheek meat, we'd love to--

DR. BERNARD: Probably not in the public domain.

DR. POWELL: That's what I'm getting at. I'll flash the FSIS document number again.

Any other comments regarding this? If not, we'd like to move on to the preparation questions. A similar sort of question, and maybe we can already guess at what you might respond, but has to do with modeling, again, outside of the anchored zone. Rather than modeling beyond the last point where validation is currently possible, that is in raw ground beef where we don't have another independent validation point until we get to human illnesses, would it be preferable to simply consider a proportional relationship at that point between the prevalence of 0157 in raw ground beef and the incidence of 0157 illnesses due to ground beef?

MS. OLIVER: Any comments on that? Dale?

DR. HANCOCK: Dale Hancock, Washington State. It seems to me that it would have to incorporate more than just simple prevalence in ground beef, have some sort of concentration distribution, or at least something that is a proxy for that because it seems possible to me that as time goes on that we'll have interventions that maybe reduce or shift the distribution down for ground beef. And that might happen at the same time we develop more sensitive methods,

for example, and so it might look like we're not making that much progress unless we have some way of inferring concentration or level of contamination.

MS. OLIVER: John?

DR. KOBAYASHI: John Kobayashi. Maybe I'm missing something in your question, but it seems to me that the occurrence of illness due to ground beef when consuming contaminated ground beef is highly dependent on the extent to which it's cooked. And consequently I think if you extrapolate from ground beef to some proportion, you're making an assumption on the level of undercooking or adequacy of cooking. I'm not sure how you can do that for a long-term model.

DR. POWELL: Mark Powell. The proportionate relationship that currently exists between the prevalence in raw ground beef and the number of illnesses is kind of the net result of all those things under current practices. But it would not necessarily be amenable to being able to predict with a great deal of certainty about what the impact would be of interventions that might change the shape of the underlying distribution curve.

If it were merely to shift it without changing the shape, then it may be reasonably useful. But if it were to change the underlying shape of the exposure distribution, such as something that would trim the tail, then perhaps not.

Chuck, why don't you weigh in?

DR. HAAS: Chuck Haas. I think by the time you go through that litany that you just ran through, Mark, you're probably adding more assumptions than you would be saving by putting the model to the state where it is now.

DR. POWELL: Mark Powell. I think the model as it currently exists involves a lot of assumptions going on between raw ground beef and consumption of ground beef. So I think we would be replacing one set of assumptions for another.

MS. OLIVER: Any other comments?

[No response.]

MS. OLIVER: Move on to the next question.

DR. POWELL: Okay.

MS. OLIVER: Skip, did you have something?

MR. SEWARD: I agree with everything.

DR. POWELL: The second question is how might we define a plausible frequency distribution for extreme time/temperature handling conditions in the absence of data? Wayne has elaborated the assumptions regarding least compliant, uniformly compliant, most compliant, in the absence of data. And I think it's an approach that reflects our uncertainty, but we'd entertain or invite your comments about how we might improve that approach.

MS. OLIVER: John?

DR. KVENBERG: I could offer two possible suggestions that may be useful to you. One is that states do two things. They do food inspections and they do outbreak investigations at the local level. Relative to outbreak investigational studies, I know of places like New York where they will go to the root cause of the investigation and make determinations on what conditions existed that contributed as a factor to the outbreak.

Secondly, at least some key states are tracking compliance with their requirements through certain critical

factors that are addressed in the Food Code, to include refrigeration, cooking temperatures, temperature abuse, hot-holding, et cetera. It may be possible through their databases to get some information relative to developing a plausible frequency of extreme conditions you're seeking on a limited basis and then make some assumptions from that.

DR. POWELL: Thank you, good suggestion.

MS. OLIVER: Dane?

DR. BERNARD: Dane Bernard. I think you had kind of part of my message before. I apologize for maybe being too abrupt at that point in time. However, I think you have to look at what we do know about the growth of 0157 as a starting point. If it doesn't grow below 8 C, then let's not model below that. It just doesn't make sense. And I think you need to look at your assumptions on lag time in terms of when you begin to lop off lag time and count that toward when the organism might start to grow. I think there are some assumptions that you made there that I personally wouldn't agree with.

In terms of your assumption on instant temperature equilibration, I think what you might do--I think, as you said, the rationale was while it goes into a refrigerator, it has got to cool down. So, you know, you think it might null out. But once the beef is chilled, the quality concerns of the industry are to keep it cold. Even when it gets out and it gets fabbed, we're doing that in cold rooms.

So I think if you look even within the agency at what kind of temperature profiles the agency allows, trim, for example--and while practices vary, the custom in most of the larger operations which produce the bulk of our beef is to put trim in, put a layer of CO2 ice in, put more trim, more ice, more trim, and they keep it cold and it goes back into a 36-degree room. So it just simply struck me as maybe a bit out of the ordinary to assume instant equilibration when we're storing at 36 in a 2,000-pound combo to assume that it goes instantly to room temperature as it affects growth.

So I think if you look at what the ordinary practices are--and there's plenty of information in the agency to give you, I think, a better, more plausible distribution in terms of time/temperature handling.

MS. OLIVER: John?

DR. KOBAYASHI: John Kobayashi. I'm not sure if this is what you're looking for because it's related to time and temperature violations in foodborne disease in general, not specifically to meat and not specifically related to 0157. But there are a couple of studies out there that relate to time and temperature violations and other sort of critical item violations in the risk of foodborne disease.

One was published around 1987 in the American Journal of Public Health. The first author was Irwin, and what we did is we looked at restaurant inspections before the outbreak occurred--we were able to do that retrospectively because of computerized records--and the occurrence of foodborne outbreaks in Seattle, Washington, compared with restaurant inspections that were done on unaffected restaurants. And there were odds ratios and that sort of stuff that occurred if inadequate refrigeration--your risk of a foodborne outbreak increased by thus and such.

Since that time, there's an EIS officer named

Bucholtz in L.A. County who did the same study, except with L.A. County data, which is considerably more abundant. And I haven't seen his data, but I've heard he came up with basically the same conclusions. But, again, this isn't related specifically to 0157. This is foodborne in general, but maybe you can extrapolate if you're needing that type of stuff.

MS. OLIVER: Dick?

DR. POWELL: Pardon me. I just had a follow-up question. Would that help us get at the prevalence of abusive conditions or the risk associated with abusive conditions?

DR. KOBAYASHI: Well, yes. I don't know. You'll have to look at some of the data and think about it. I mean, basically we were able to get odds ratios in attributable risks involved, and I think they did the same thing in L.A.

DR. POWELL: Thank you.

DR. KOBAYASHI: But, again, it's restaurants and not slaughterhouses, and so forth.

MS. OLIVER: Dick?

DR. WHITING: Dick Whiting, FDA. I would echo some of the comments I've heard recently on the use of lag times in some of this. Maybe you've got organisms that some might be adjusted to the intestinal tract and then you've got other organisms that have dried out on the skin. I think the conservative approach is to sort of disregard the lag phase and just assume the organisms can grow.

Another comment. I'm not sure just exactly how you did model temperature, and so on, but we did come across some data in our studies on the temperature in home refrigerators. And if that would be of use for you, I can supply that.

MS. OLIVER: Dale?

DR. HANCOCK: Dale Hancock, Washington State. It seems to me to estimate how common those extreme things are, couldn't bacteriological profiles at the retail level give you some information about what fraction of ground beef has been seriously temperature-abused? Maybe Dr. Gill can provide more insight on that?

MS. OLIVER: Colin?

DR. GILL: We're just in the process of completing a rather extensive study of the cold chain in Canada. It turns out that all the products have reached temperatures below 6 degrees centigrade by about 7 days, but it takes 7 days to get down there. After that, we found no product above 6 degrees centigrade until it got to the retail level, on display, when 4 percent of the products at any time is above 7 degrees centigrade.

So the only time that you see to be getting temperature abuse to any extent in the general distribution is in the cooling down phase, after the carcass is broken up, and when it's return to the retail shelf. We've also looked at combo bins and those are, of course, brought down, as you say, with dry ice. And they were uniformly below 6 degrees centigrade. So, basically, until it gets to the retail level or to perhaps the restaurant level, you haven't got much of a problem as far as temperature is concerned, apparently.

MS. OLIVER: Isabel?

DR. WALLS: Isabel Walls, NFPA. I'd like to agree

with what Dane said, and also just to urge caution using modeling data. There are so many unknowns here. I think it's helpful to use modeling data for "what if" scenarios, but we don't really know how long products are temperature-abused, although there's some evidence now coming out. We don't have a lot of data on how many people are abusing these products.

So there's a lot of unknowns, a lot of assumptions that could adversely the model, so I'd just urge caution in doing it. It may be helpful or interesting to do some "what if" scenarios. What if it is abused? But, you know, unless we have really good data on how much is abused and at what temperatures, you may not want to use it in the model.

MS. OLIVER: Any other comments on this point?

[No response.]

MS. OLIVER: Do you want to move on to the next question?

DR. POWELL: Thanks. Finally, we'll turn to the set of questions regarding dose-response, and we would ask whether the Committee feels that there are sufficient data methods currently available to develop a separate dose-response relationship for the susceptible population and how we might validate such a dose-response curve.

MS. OLIVER: Any comments?

Chuck?

DR. HAAS: Chuck Haas. There is not data that I'm aware of, and I think the only approach to getting such data will be to develop animal models and to do the test on an animal model susceptible sub-population.

MS. OLIVER: John?

DR. KOBAYASHI: John Kobayashi. If by a susceptible population you're talking about children, I agree. I'm not sure that there's that much data out there, but a couple of things that come to mind is that maybe you can tease something out of the '93 outbreak, making the assumption that those were children's burgers and most of the people who ate them were children, as opposed to small adults or, you know, adults who were eating small amounts of food, and then break apart--there should be an age distribution, and so forth, with regard to the cases, and so forth.

The other thing you might want to look at is that there were two waterborne outbreaks, one in Alpine, Wyoming, related to 0157:H7, and another one in Missouri many years ago. And in that case, you had a whole community, young and old, et cetera, that were exposed to contaminated water. And maybe there's some way of looking at the differential occurrence with regard to the illness by age. I think one of the problems with just looking at raw surveillance data is how much of an influence exposure has on the age of occurrence of the cases.

MS. OLIVER: Chuck?

DR. HAAS: Chuck Haas. I'm familiar with both of those waterborne outbreaks. In Kabul, that actually, as far as I understand, preceded the ability to measure 0157 in water samples, and so there simply are no water data available. For Alpine, the people I've talked to say they've been unable to isolate 0157 from the water sample, so again we lack exposure data.

MS. OLIVER: Can you identify yourself and talk into the mike, please?

MS. COLEMAN: Peg Coleman. Just a follow-up question on waterborne outbreaks. Wasn't there an outbreak in New York this year?

DR. HAAS: There was, and I haven't heard any indication as to whether or not they've got exposure data for that.

DR. KOBAYASHI: This is John Kobayashi. I do know that they got the 0157 out of the water, and I assume they quantitated it. But then the question is the population exposed and how well they were able to define that because it was a big state fair or something like that.

DR. POWELL: A lot.

MS. OLIVER: Any other comments on this?

[No response.]

DR. POWELL: So moving on to the next--

DR. HULEBAK: Just one point. I did talk to Nancy Strockbine and Paul Mead before they left and they've promised us that they will be submitting some comments by e-mail, anyway, in written form, to help address some of these questions. And I should reiterate that that invitation stands for all members of the Committee and invited experts to give us your thinking, any other thoughts that you have in the next couple of months.

MS. OLIVER: Do you want to move on, then?

DR. POWELL: Thank you, yes. The next question-- I'm sorry that Margaret seems to have left because she had a comment earlier regarding the applicability of the EHEC to define the lower bound of the envelope. But we'd ask whether the Committee thinks that the bounding approach used in the envelope methods, using *Shigella dysenteriae* as the upper bound and the EPECs as the lower bound--whether that approach is sound and is reasonably likely to capture 0157 somewhere within those bounds?

MS. OLIVER: Does anyone on the Committee or any of the invited experts have any comment on that?

Chuck?

DR. HAAS: Chuck Haas. I'm starting to think although it certainly was reasonable to begin with that probably the *Shigella* may be simply much more potent. That may be over-conservative in terms of estimating the upper bound.

MS. OLIVER: Any other thoughts or comments?

[No response.]

MS. OLIVER: I don't see any.

DR. POWELL: And then finally the one dose-response curve that did have the greatest extent of overlap with the epidemiologic curve obviously is anchored, and so it has kind of a leg up on a more uninformed approach. But on the other hand, we think that if you've got data, you ought to use it, is another argument. And it flows from ideas about, you know, kind of most likely estimation sorts of procedures, where you want to--or maximum likelihood procedures where you want to say what values for the parameters are most likely, given the available data. So we would ask your comments as to whether you think that that sort of an anchoring approach was appropriate.

MS. OLIVER: Does the Committee have any comments on that?

DR. POWELL: Well, if Chuck Haas shrugs, we'll take that as a--

DR. HAAS: Chuck Haas. You know, I'm comfortable

with it because as I mentioned to you before one-on-one, it looks like that dose-response curve probably overlaps the animal dose-response curve that exists. So, you know, I'm comfortable that it's giving reasonable-looking results.

DR. POWELL: Dane?

MS. OLIVER: Dane?

DR. BERNARD: Dane Bernard. This is obviously a question more appropriate to the modelers than the non-modeler food technologists. The only thing I would ask is that you, in your descriptive terms, do some ground-proofing on it by looking at what has happened with outbreaks, what we do know about outbreaks in terms of what may have been there even though there are methodology differences and there are gaps and there are holes.

I go back to what I said earlier that we seem to have run into--the problems come from outbreaks and clusters, from what we know, and we seem to have probably presented a good deal more 0157 than we have problems. So just try to take what is there and look at it practically and see whether the anchor that you've picked makes sense in terms of what we're observing in practice. And you're puzzled and I don't know how to go any further to answer the puzzled look on your face.

DR. POWELL: Mark Powell. Well, looking at the active surveillance data suggests that most of the cases of 0157 are sporadic rather than associated with outbreaks. And clearly I think we would do well to follow your advice by trying to explore more fully the kind of extreme events that could lead to big doses or a large population being exposed and what sorts of steps in the process lead to those extreme outcomes.

MS. OLIVER: Any other comments, Chuck?

DR. HAAS: Yes. Chuck Haas. I'm not quite comfortable with the argument that most of the case burden is from outbreaks. And, you know, let me throw one other piece of data on the table. The data that has been reported in England and Wales--they report 0157 confirmed outbreak cases and total laboratory reports, and they show a ratio of about 10-fold between them.

You know, I think most people believe that England and Wales probably captures a greater proportion of outbreak in their reporting system than we do. So, you know, I would use that possibly as a lower bound for ratio. I think there are a lot more sporadic cases or unreported outbreak cases than reported outbreaks.

MS. OLIVER: Dane?

DR. BERNARD: Dane Bernard. I'm not going to get into a war with Chuck over this. I would agree. You know, my intuition says that a lot of the sporadic cases are just outbreaks that we haven't linked up. So I guess that's kind of where I was coming from with that.

But, you know, with the ratio that you've developed in terms of the total number of cases that are due to ground beef--that was, what, 17 or 18 percent--if you look at that, that kind of narrows down the total case burden. And I do think that we're going to be getting better at linking things together, which still leaves me uncomfortable at looking at this just as a general problem with leaving out that hump out there, that unusual event that contributed to those outbreaks. That was my only point.

MS. OLIVER: Any other thoughts?
Colin?

DR. GILL: If the distribution of cases is sporadic, aren't you just seeing the upper end of a distribution of an organism that's present at very low numbers? You're just seeing the normal distribution with a large standard deviation and you're seeing the top 0.1 percent.

MS. OLIVER: Jim?

DR. ANDERS: Jim Anders, North Dakota Health Department. And I'm from the laboratories, by the way, and so I'll speak from the laboratory point of view here, from a public health laboratory. As far as the cases that we get-- and, of course, North Dakota is not very heavily populated, but from the numbers that we're getting of 0157:H7, almost all of them are not related to outbreaks, okay, that can be traced to outbreaks, per se.

So I don't know what that means, other than that's what we're seeing. And I can't speak for some of the other states, but basically we get them here and there, and when they check them out, they do not seem to be related to outbreaks.

MS. OLIVER: Any other comments?

[No response.]

MS. OLIVER: Okay. Did you have any other questions for the group?

DR. POWELL: None at this time, no--

MS. OLIVER: Okay.

DR. POWELL: --although we reserve the right to come back to you with more questions.

MS. OLIVER: Fine.

I'd really like to thank the group for all of your input, thank the Committee and the experts for all of the input. It has been very beneficial to both agencies and we really appreciate it. And we really appreciate the long days that you've had to put in. Some of you have had to endure three days, and have endured it. We appreciate that.

We will be having a meeting in the spring of the Advisory Committee. We haven't quite gotten the agenda and the topics together yet, and Dr. Wachsmuth and I need to talk about that. I'd like to wish you all a safe trip home, and enjoy your holidays.

[Whereupon, at 4:59 p.m., the meeting of the Advisory Committee was concluded.]

[Home](#) | [HACCP](#)

Hypertext updated by cjm/dms 2000-JAN-27