161 of them were known to have been destroyed in a way that did not allow for animal or human exposure. 173 of them we didn't know that for sure.

Interestingly, others, for example, in the GBR for the United States, it was assumed that any animal imported before 1986 was perfectly safe. I mean, in that way I think we were a little bit harder on the U.S. than even the Europeans were because we said we're not at all comfortable saying that.

You saw those graphs from Maura Ricketts of the projections of the rate of the disease prior to it even being found. We looked at those kind of data and using information on the birth year of an animal and the rate of BSE in their birth cohort, the year in which they left the UK, the kind of animal it was, which influences its likely exposure to protein products in the UK, when it was last seen; that is, how old was it at least when it was last seen.

We don't know in some cases what ended up happening to that. We can look at those knowing something about the progression of the disease, the incubation period of the disease, and we can make some predictions about the likelihood that that animal could have brought infectivity in the United States and could have been introduced to U.S. cattle feed.

Then what we did was use our model to say what would happen if we, indeed, had introduced -- made these introductions into the U.S. What we found is that there is based on what we know about those animals that came in, our estimate was somewhere in the order of an 80 to 85 percent chance that there was, in fact, no infectivity introduced in U.S. cattle feed from those animals that came from the UK.

Most of the introductions that might have happened give no new cases. They are very, very small introductions. Perhaps small enough that they wouldn't have caused disease.

Surveillance, and this gets to Ermias' question. Surveillance rules out some of the very big introductions. We couldn't have had a lot come in here because we went 15 years with no feed ban and our model, if you put in a lot of infectivity for 15 years with no feed ban, you get a lot of cases of BSE, more than we could probably have and not have found the disease yet.

The other thing that is interesting is the way we model those things changed over time and, in fact, we started the -- for example, we started our simulations. Instead of doing 20 years we did 30 years and we started it in 1980. We followed the U.S.

risk management measures, for example, and we put in a feed ban in 1997. We assumed that it was reasonably complied with but not very well for a couple of years. Compliance got a little tighter after a couple of years sort of to our base case level and we watched it go. Interestingly, even if it wasn't introduced from the UK, which we're saying it could have happened.

It could be again at a level that we couldn't detect. Even if that happened, again, these measures in place are eliminating it from the system. Again, the feed ban is preventing serious recycling of infectivity.

This is just our estimate that is 82 percent chance that there was no infectivity introduced. Then these others are the number of cattle oral ID_{50}s from those English animals that could have been introduced.

This then says what if some number of those would have been introduced. That horizontal line there is our estimate of the year 2000 sensitivity of -- actually, this is the USDA's estimate of sensitivity of their surveillance.

Each of those says for the introduction of different numbers of ID_{50}s how many clinical cases might we have had in the year 2000. So what it's

showing is that in many cases with an introduction there were no new cases. The amount wasn't right. It was given to too many animals. It was too delude.

When there were cases, everything above here we quite likely would have detected. We can kind of rule those out but we have this area right in here of situations in which there could be some cases and we cannot be certain that our surveillance would have found them.

Again, if this happened, this is the year 2000. If you think back to those graphs a while ago, the disease is on its way out and would be eliminated again somewhere on the order of another 10 years. That is primarily due, virtually entirely due to the FDA feed ban even with incomplete compliance.

Quickly, some other results. We looked at Switzerland. We touched on this briefly as a test of model plausibility. We underestimated by about 50 percent the number of clinical cases. They had approximately 400 and we estimated in the order of 180. The time course, however, was followed quite closely. Between those two things we think that at least the structure of the model is working in such a way that it has some plausibility.

We looked at this question of spontaneous

BSE. Could there be spontaneous BSE in the United States? We modeled the spontaneous disease on sporadic CJD. As you know, sporadic CJD has on average across the population a rate of roughly one per million in populations around the world.

Of course, that hides the age structure of the disease, the fact that it's virtually never seen in people under about 50 years of age. The rate peaks somewhere around 75 to 80 depending on which country you are in and kind of tails off again.

We said what if that exact same age structure applies to the American cattle herd. We know something about the age structure of the American cattle herd. How often would we expect spontaneous disease to arise in the United States?

When we do that, if spontaneous is true, and there is no certainty whether or not that is the case, in that situation we would have a mean, an average of about two cases of BSE per year in the United States from spontaneous disease and about 100 cattle oral ID_{50}s for potential human exposure over 20 years.

What that says is we will never know. Two per year will never be found so it could be happening. It's happening at a relatively low rate and one of the

reasons for that is the U.S. cattle herd has very different demographics than those in a lot of other countries.

We have a very young herd. Not as young as the UK does now but our cattle herd doesn't have nearly as many animals that get out into the advanced ages where if human sporadic CJD is a good model for spontaneous disease, it would be expected to be occurring at higher rates. For that reason we predict -- the model suggest there would be about two cases per year.

Now, one of the things we did is we also said what if this in fact was the case in 1980 and we modeled the United States in 1980 with no feed ban and pretty heavy use of animal protein and looked to see what happens. What happens is it blows up.

If we just sort of say the world is chunking along in 1980 boom, spontaneous disease starts to happen in the United States, those first two cases in the first year give rise to some more cases because they are recycled.

The two new spontaneous cases then give rise to more and it blows up. Over 20 years we get up to a situation in which it would presumably be at a detectable level in the United States. This, to us,

cast a little bit of doubt on the plausibility of this particular hypothesis.

Now, there are particular situations in our model where we could have had spontaneous disease, not detected it, and the feed ban is also sort of moderating the effect of any disease that might have spread that way. We cannot rule that out.

We also looked at scrapie using data on estimates of the rate of scrapie in the United States. The recycling of sheep, the potential of that material to contaminate cattle feed, etc. Again, we come out with a mean prediction of roughly two BSE cases per year from scrapie in the United States based on the assumptions that we make about the rate of scrapie and the species barrier and things like that. Again, this could percolate along, two cases a year, never be detected and we wouldn't know. It's not a large amount but that's what could happen.

Again, it's not in the report but you can imagine that if we introduced scrapie in 1980 with no feed ban, it would also flow up to a significant extent in the United States.

In summary, we have tried to look at the potential for BSE infectivity to spread in the U.S. if it were to arise and we look at that arising either

from imports, from an endogenous or spontaneous TSE, or by importation. We have used our simulation model to sort of look at what are the pathways that give rise to the greatest likelihood of spread, what are things that are doing a lot to prevent the spread.

I guess one of the findings that was most interesting to us is that the U.S. is resistant to BSE meaning that it does not -- it is very difficult to find any plausible set of assumptions under which the disease becomes established. For that reason, most of the time even following an introduction the disease dies out in the United States.

Human exposure to infectious cattle tissue is relatively low. Again, this is a potential human exposure and, again, it's through either consumption of known specified risk materials like brain or spinal cord, or that potential for contamination of certain kinds of products.

Spread in the cattle herd is almost entirely influenced by the compliance with the FDA feed ban. There is potentially some maternal transmission and we include that in our model that if a cow, calves near the end of the incubation period there is about a 10 percent chance of her passing that disease onto her offspring.

The animals that die on the farm in our model presumably with BSE inject the greatest amount of infectivity into the system. For potential human exposure the handling of brain and spinal cord in processing is very important including, for example, whether or not people comply with a directive from the USDA that says if you are going to use these advanced meat recovery systems, you have to remove the spinal cord. Anytime that isn't done, that allows the potential for infectivity to be introduced into that product.

The primary roots of exposure for people, just as I've said, cattle brain, spinal cord, beef on bone, again with the caveat that that includes things like spinal cord and dorsal root ganglia that may or may not be consumed. Then finally advanced meat recovery product.

Those animals that came in from the UK between -- well, we looked at only England -- came in from England between 1980 and 1989 do have a small chance of having introduced BSE into the U.S. herd. If they did, the measures that are in place subsequently should be eliminating the disease in the same way they would with an introduction that would occur today.

We reasonably mimicked the Swiss BSE outbreak and gives us some confidence in our work. We looked at this cross-species transmission of scrapie or spontaneous BSE. If they are real, today in the United States we could give rise to a few cases over time and relatively small amounts of infectivity that could potentially be available for human exposure.

We also think that our model by looking, for example, at the specified risk material ban it's useful for evaluating potential risk management strategies that could be taken in the future. You could design all sorts of things and look to see quantitatively how they would influence the likelihood of spread in animal herd or the likelihood of people being exposed.

With that, I'll stop and thank you.

CHAIRMAN BOLTON: Well, thank you very much, Dr. Gray. We will now open this up to questions. I'm sure there will be a few.

Ermias.

DR. BELAY: George, you may have addressed this issue sometime in the past but you finally modeled the international BSE through importation of animals. What if BSE was introduced into the United States through meat and bone meal or MBM? Would that

change your predictions?

DR. GRAY: I don't know if you heard the question Ermias asked. Our way of introducing BSE into our model, when we assume the U.S. has none, is through infected animals. Would it be different if we introduced it through meat and bone meal? The answer is qualitatively no. In essence, bringing in a sick cow is just like bringing in a load of meat and bone meal.

Then it is spread out and we look to see how it propagates through the system. Qualitatively it would not be different. Quantitatively it wouldn't matter how much infectivity we felt was in that meat and bone meal, how often it came in, how many shipments, sort of how much it was and how many animals it was spread to.

We would still end up with a situation in which there would be relatively few new animals infected compared to the original -- well, there would be relatively little new infection but there would be some because of leaks in the feed ban and other such things. The feed ban would be eliminating the disease again. Qualitatively it would look the same. Quantitatively it would look different.

CHAIRMAN BOLTON: Peter.

DR. LURIE: I think the question is excellent. It's hard really to know what to make of the answer to it because the amount of -- the number of ID_{50}s that could be brought in through meat and bone meal is potentially very, very large and much larger than would be included in 10 infected cattle.

Your 10 infected cattle can be said to be equal to some amount of meat and bone meal but it's quite possible -- it's much more likely it seems to me that meat and bone meal might have gotten into this country than cattle. Those are easy to detect.

Especially because we of necessity have been behind the 8 ball in terms of the countries from which we prevent the importation of meat and bone meal. There were exports of meat and bone meal from Japan and countries in Europe before they were known to have BSE cases.

Then later on it turns out there was, in fact, BSE in the herd and the material has already been distributed. I think the meat and bone meal question is an excellent one and I'm not sure that your answer quite gets to it.

DR. GRAY: Oh, sure. The answer is qualitatively the results are going to look very similar. There are a lot of subtleties and nuances.

If we introduce meat and bone meal the very important thing is how many animals is it introduced to.

If it's got lots of ID_{50}s and we give it all to one, that's going to have very different implications than if we introduce it to 1,000. There are things that cut in both directions. Quantitatively, as I said, it will look different than introducing the cattle.

Qualitatively it is still going to have the same situation in that those cases that would be caused by that you could then think of as now we've got those 10 animals or those 100 animals or those 500 animals that we modeled and the same thing would happen. You would have some new cases but the disease, again, would gradually be eliminated by the presence of the feed ban.

DR. LURIE: Unless the numbers are 10,000.

DR. GRAY: Ten thousand would take a long time but it would still -- it would be very different. Also then you would have questions with the consistently of our surveillance, for example.

CHAIRMAN BOLTON: I think that may be a moot point. I wish Linda Detwiler were here but I think that we were not a significant importer of meat and bone meal.

DR. FERGUSON: That's very accurate. Yes, we were not significant importers of meat and bone meal.

CHAIRMAN BOLTON: I think we were actually exporters.

DR. GRAY: We're a net exporter by far.

DR. FERGUSON: Correct.

DR. GRAY: And when we import it, it tends to be stuff like lamb meal from Australia.

DR. FERGUSON: Actually, we have made every effort to obtain as much information as possible as many years after the fact on all of these shipments that are recorded in Customs database under anything remotely resembling a code that could be considered meat and bone meal. What we're finding is, yes, there are some shipments that came in. These were legal shipments that came in.

For a period of time there were significant quantities of a porcine collagen binder from Denmark and from Sweden that was going into pet food. There is poultry meal coming in and going into pet food. Specialized products essentially going into pet food. There's really not a risk there that we can see.

CHAIRMAN BOLTON: Dick.

DR. JOHNSON: I worry about the wild cards that may impact such a model. If we were asked to design a model of what would happen if scrapie got into cattle back in 1982, none of us would have come up with that crazy idea of rendering.

Did you put some of these things into the model like the prevalence of poultry litter feeding, a low consistent level of horizontal spread that may be there that is buried by the epidemic of the sort of nature that we see with scrapie and chronic wasting disease? Did you look at recycling with the table scrap exclusion and so forth?

DR. GRAY: We looked quite closely at the FDA feed ban including things like the use of porcine and equine protein, the use of plate waste and other exceptions there. Those you can read in the report. As we look at them quantitatively they are unlikely to be major sources of recycling and you can look at them.

DR. JOHNSON: Poultry litter isn't --

DR. GRAY: Poultry litter is one --

DR. JOHNSON: It's an ovine. Poultry litter is ovine.

DR. GRAY: Poultry litter is one that -- I was coming to that. That is one where we actually

didn't become aware of that until quite near the end of our work and, frankly, all we have is a couple of sentences in the report that say this is something that somebody has got to look at because that's one where you don't have multiple rendering steps. You don't know and there is the potential for --

DR. JOHNSON: It is apparently largely informal trading your poultry litter with the guy next door with the cow. Do we have any survey of any idea of how many people feed poultry litter and how much of it gets fed?

DR. GRAY: We certainly have come across nothing like that. You could ask FDA. I don't know and I don't know if anyone does.

DR. JOHNSON: I get the impression in the FDA quite a lot of it goes on surprisingly but on an informal basis.

DR. FERGUSON: I think there are some areas of the country where, yeah, quite a bit of it goes on.

DR. JOHNSON: It's regional, is it?

DR. FERGUSON: Well, obviously, I mean, you're going to be doing it in areas where it is a significant poultry production area.

DR. JOHNSON: Since it's disgusting you

better not say which regions they are.

DR. FERGUSON: I won't. I won't. I don't know that I would necessarily say it's informal, though.

CHAIRMAN BOLTON: I have a question. You have looked at the feed ban as a major variable in terms of its effect on the outcomes. What other parameters when varied have similar kinds of effects as the feed ban? I mean, if you look -- you've got a model that must have perhaps literally thousands of different variables. Which ones have similar kinds of effects on the outcome?

DR. GRAY: That's a good question. It turns out to be -- well, some of them that you would expect and some you wouldn't. I mean, one thing, for example, that we have in our model is once the disease is in the country and circulating if it were introduced, how good would inspectors be at finding it at an ante mortem inspection.

That makes a very big difference because if an animal is at the stage of clinical disease gets to inspection and that inspector doesn't catch it, that is a lot of ID_{50}s that are going into the system. We have no way to estimate how likely it is that we would do a good job of finding -- of detecting it on

ante mortem inspection.

For example, that's something that makes a pretty big influence on how much infectivity could ultimately get to people before letting sick animals in. These rates of misfeeding, these things that are related to the feed ban tend to be the ones that have the biggest influence on spread in animals.

Things that are related to measures that would keep specific high-risk materials out of the human food supply are the ones that have the biggest effect on humans. Again, it's compliance with the USDA FSIS directive to remove spinal cord from advance meat recovery. Most of it ends up being pretty intuitive.

CHAIRMAN BOLTON: Other questions?

DR. FERGUSON: Not a question but I feel compelled to sort of put a plug in here for the Department of Agriculture, those that pay my salary. Anyway, if anybody is interested in reading the entire report, if you didn't know, it actually is up on our website. When I say our website, that is USDA APHIS. I believe FSIS also has it on their website, www.aphis.usda.gov.

Also on that website you'll find some details about what the Department is considering doing

sort of as a result of some of the recommendations, some of the results of the Harvard assessment.

DR. JOHNSON: A warning came out when that was posted from several people saying it crashed their computer when they downloaded it. I was afraid to do it.

DR. FERGUSON: Actually, it is true. There is some truth to it because it crashed our computers when they sent it to us but it's only one part of the report. If you look on our website, it's broken down into several parts and it's the section that has all of the figures and the graphs. We had to have a media people print it out because they have those types of computers.

CHAIRMAN BOLTON: I want to know if that crash was caused by a prion or a virus.

DR. FERGUSON: We don't know.

CHAIRMAN BOLTON: You don't know? Okay. Peter.

DR. LURIE: I guess models like this obviously are only as good as the data that go into it. Obviously reasonable people could disagree with a particular assumptions that went into this.

Dick, you in particular, for an example of this is the plate waste one where it's not really in

the model. I mean, it's out of the model because you assume that the risk is zero. Right? I think that's correct.

There are assumptions like that which will obviously have to be examined. You might well be able to justify that it's zero. I'm correct about that. Am I not?

DR. GRAY: Well, we don't assume it's zero but one of the things that we've worked very hard to do is to lay out on the table everything that we assumed and considered why we thought that was the case. We also have in many cases the alternate ideas that someone might have so if anyone wanted to look at it in another way, they could.

For example, in the case of plate waste there are a variety of reasons to think that if it were introducing infectivity or the potential for recycling of infectivity, it would be a very, very small amount compared to the many other routes that are around. Again, that is our assumption and we lay it out.

DR. LURIE: I guess the other thing in looking at the report that struck me is all through this whole epidemic what we are really dealing with is the possibility of low probability events with

catastrophic outcomes. That is really, to me, a lot of what we are dealing with here. Even the blood issue is very much like that. It seems that the probability is low.

On the other hand, if we are wrong, then it could be terrible because the exposure is high. The reason I make this point is that it is fine to present, as you do, what your base case analysis is with averages and even 95th percentiles. But in many ways what we are really worried about is the absolute worse case scenario.

As I read the report, once you start looking at 99 percentiles, which are obviously less likely to happen than 95th percentiles, very terrible things start to happen relatively quickly. The point is that the variables are very, very skewed of necessary. You do one way sensitivity analyses which is to say as I read it that one at a time you do them, which is to say you think of one thing kind of going wrong at a time.

What I'm worried about is if, in fact, the worst end of the skew turns out to be the case and two things go wrong at a time. Once that happens, then the scenario becomes less reassuring than your base cases.

DR. GRAY: We can talk about this in a lot of detail. Perhaps the best thing is we'll give you the model and you can go crazy. We are very willing to share this and to let anybody who wants to change whatever they want to do, make whatever assumptions they want to do.

DR. LURIE: There's nothing incorrect about what I just said, is there?

DR. GRAY: There's some technical things that are incorrect but we can talk about those later. I mean, about particular percentiles, the distribution and the ways in which you estimate them. We can talk about those.

CHAIRMAN BOLTON: Other questions? Did you want to make a statement?

DR. GRAY: No, no.

CHAIRMAN BOLTON: I heard a voice from somewhere coming out of the blue.

DR. GRAY: I'm here to answer questions.

CHAIRMAN BOLTON: Questions from the audience or comments? Well, very good.

Dr. Gray, thank you very much. I appreciate that. It's been most enlightening.

I believe at this point we are done. If there are any other comments or questions from the

committee, I will entertain them now. Otherwise, I would move to adjourn the meeting. Stand adjourned. Thank you.

EXECUTIVE SECRETARY FREAS: I would just like to thank everybody for coming here, the BPAC for two days, TSE for today. I would especially like to thank our chairman for getting us through this discussion.

(Whereupon, at 4:35 p.m. the meeting was adjourned.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: Meeting of the TSE and Blood Products Advisory Committees

Before: DHHS/FDA

Date: January 17, 2002

Place: Bethesda, MD

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.