States have pretty much been in sync with their regulations but we realize that there is so much trade between the three countries in North America that we had to really fine tune it. So we've worked for the last year and a half to make a uniform I should say North American policy in regards to import restrictions. Next please.

Just again to give you an idea of what products here, unrestricted entry and these are because of scientific reasons of no detectible infectivity, milk and milk products, semen, hides and skins, tallow and tallow derivatives and they would be tallow that is protein free prepared so that it's protein free, and this is in accordance with the guidelines from the Office of International Epizootics and then WHO. Just for those that don't know, the OIE is kind of the animal equivalent to the WHO. Next please.

For other products, we have restricted entries. They can be totally prohibited. They can be for in vitro use only. The importation of raw materials into a restricted country for manufactured products, then to come back into the U.S. and under permit conditions for scientific or research purposes. Let me just give you an example of the

third here. We have some individuals in the United States that do better with bovine insulin produced from bovine. There's a plant apparently they get it from in the UK but now what's happened is that we send the bovine pancreases over from the United States, it gets processed under certain restrictions and comes back to those individuals, okay, under permit and under supervision. Next please.

The restricted entry blood, fetal bovine serum, bovine serum albumin is prohibited into the United States for use in any kind of animal, pharmaceutical, biologics, heparin, lipids, tissue extracts and gelatin are prohibited. And then under some restrictions microbiological media with ruminant-derived products and then collagen-derived asituants, chondroitin sulfate is prohibited. Next please.

You've probably seen enough on this. I put this in because I wasn't sure how much Bob was going to cover on the number of cases from the UK. Next please.

And this is just the epidemic curve which you've seen several times and just the whole numbers of confirmed cases of BSE throughout the world. Again you can see right now the native cases

of BSE have been confined to Europe, European countries. There have been cattle that have been exported outside of Europe such as Canada, Oman, Falkland Islands, but these were imported animals into those countries. Next please.

I just wanted to point out on this slide here why we took the entirety of Europe restriction or prohibition. In 1997, Netherlands, Belgium and Luxembourg reported their first cases of BSE despite BSE being known in the world since 1986, and when we looked at especially Belgium, the Belgium cases, what we saw is that really because of the trade within Europe and how the European Union, the movement and that they can't put restrictions unless the community says that the product and live animals were moving between countries. Another thing that we looked at is surveillance and how much surveillance was being conducted, and Dr. Heim really pointed out the amount of BSE really depends on the quality of your surveillance system and in fact, how much you actually, even the clinical, get reported prior to Switzerland doing the targeted surveillance. So when we look at those two factors, we really did say Netherlands and Belgium were no more a risk for us the day they reported BSE versus

the day, weeks, months before and so we thought that we better stop the trade with Europe until we could ascertain if there were any real differences between the countries or even other countries of the world.

And to go back before I get into this a little bit more, even with Canada and Mexico, now we have an agreement between the three countries that any of the countries we trade with, that we will evaluate those even if they are outside of Europe to look at their risk factors regarding BSE.

These are just some epidemic curves in the countries. One thing to point out, they're not ont he same scale. The top for Ireland is 100, Switzerland is 80, Portugal is 200, and then France is 35. So you can see but one of the things that's also been pointed out that I want to point out is that in 1999, these countries have recorded the highest amounts of cases in other than in previous years. So I think that's important just to note that and that's even without other than Switzerland without these targeted surveillance which actually Europe is now moving towards. The European Union and Dr. Heim can jump in or correct me, has adopted policy that countries are supposed to go to targeting the populations like Switzerland and then

conducting these tests. Next one.

This you've also seen. This is the incident rate per million cattle in over two years of age. Next please.

Now to go back to the U.S. BSE import prohibitions and how we did, we prohibited in 1997 the live ruminant and most ruminant products from the entirety of Europe because of the trade and surveillance but we did say to the countries we invited them in our interim rule to submit data to look at what risks they had and the risk mitigation measures. Okay. And now that's been extended to other countries of the world. So at that time we asked them to provide data. So what did you import as far as cattle, MBM from countries known to have BSE? And also it's important I think, Dr. Schonberger had pointed it out, that a lot depends on the mitigation they've done for not only human exposure but also animal because in the bottom line the more you prevent the animal exposure, you prevent human because if your animals aren't infected then your humans won't be, and I know the Department of Ag, our policy is keep it out of our cattle and then we'll keep it out of our humans.

So what we did is we based our criteria

to do our assessment on the OIE or the Office of International Epizootics standards and basically what they required is that the disease is notifiable, BSE, that there is an active or surveillance program in place and they actually give guidelines for numbers that countries are supposed to look at based on the adult cattle population. So we evaluated that based on the OIE guidelines and standards and then the countries are supposed to conduct a risk assessment on the imported cattle from not only the UK but other countries known to have BSE, imported meat and bone meal and then their current training practices, who they in turn trade with. You kind of have to be careful. I think Switzerland too is a good example and what they found out. They looked initially and they said, well, we don't have too much trade with the UK. So this might be okay, but when you look at who they had trade with and then who they traded with and this movement of products and cattle, you can get a real surprise. And then ruminant feeding and then the prohibitions on the feed bans and what type of feed bans were in place. So these are the things that we did evaluate. Next please.

We had a total of 14 countries submit,

eight countries without native BSE. The remainder did have native BSE but they submitted dossiers to the USDA. Now we had evaluated those. We came up with evaluations on each of those countries and in the process of going through this, we were getting ready and writing up a rule to announce these evaluations and then the European Union started to conduct their own evaluation. And what we decided is that believe it or not, even though the two processes were very different, at least what we evaluated, the outcomes were similar but we did have some differences. So we decided before we published to kind of hold off and see Europe and see how close we are and also look at what information that both groups that evaluated got to see if they had additional or we had additional information on the countries.

And one of the differences you'll see when I talk about the European evaluation is that they have four categories, okay, in their categorization of countries, and we were going to go with two, and I'm not sure. We're still in this evaluation, a restricted versus a non-restricted. I mean don't hold us to those terms. We were debating on how to call them. Lisa's smiling because she

knows how many times we've talked about this, what to call these, but the countries that are okay to trade with for ruminant and ruminant products and those that are not. Next please.

In the European Union, perhaps some of you have seen this or most of you have seen this, just on the web I believe it was Tuesday, they posted prelim reports on their geographical BSE risk assessments. Groups there evaluated 25 countries who were member states and non-member states, or whoever wants to trade with the European Union, and in this process they examined, they kind of approached it more of like a challenge and a stability of the system approach and basically their challenge is just kind of like what we looked at, the imported cattle, okay, from UK which was considered the biggest risk and then other countries that have BSE and they were assigned like lesser and then stability of the system and what the system is is the cattle feeding system, looking at feed bans. So it would be ruminant to ruminant, mammalian to ruminant or like the United Kingdom, mammalian protein to food producing animals and so that was the feed bans, one factor of the system.

They specified risk material, if there

was specified risk material bans. That's another key component and also the time, temperature, pressure requirements of the rendering system. So they were evaluated for the system to look, and basically what they were looking for in the final outcome is how much of a challenge did you have and how stable is the system because you can have small amounts of challenge and if you have a pretty stable system, then you wouldn't expect to see BSE. If you have large amounts, a pretty stable system, but not totally, you can override it and if you have an unstable system and you have no challenge or very little challenge, then you wouldn't expect even with the unstable system that you might be able to escape. Next please.

So the categories of risk, Category I, European Union classification was highly unlikely to have BSE. Category II was unlikely but cannot be excluded. Category III was actually divided into sections, likely but not confirmed, so have high risk factors, but maybe the surveillance system wasn't considered sufficient enough to pick up the cases, and then BSE confirmed but at a lower level. That's all in Category III and Category IV is BSE confirmed at a higher level. Next please.

Category I, I'm just talking the European even though there were non-member states here, and Norway is a non-member but is part of Europe. That was the one country in Europe that was found in Category I was Norway, and again this is prelim and Norway traded with Denmark which subsequent to this evaluation reported a case of native BSE. So one of the little caveats on this prelim report said we have to look into the trade with Denmark and what happened to imported cattle and perhaps Norway would have to be classified II. So I think that's up, but right now on the prelim, Norway was in I. And basically they had very few UK imports prior to 1988. Next please.

Category II, this would be unlikely but not excluded, okay, and it would be Austria, Finland, Sweden, the Czech Republic, the Slovak Republic, and again I think Finland has the caveat too to look at meat and bone meal that might have come from the continent like mainland Netherlands and if they can't ascertain really the movement and work that out, they might move to Category III. So there was another footnote in there. Next please.

Category III, the three countries and I separated them out that are likely to have BSE

categorized but not confirmed, so likely to have it but not confirmed, would be Germany, Italy and Spain. So the three yellow little dots there and the remainder with the blue triangles, they have confirmed but at a lower level. Okay. Next please.

And Category IV, the European countries, these are BSE confirmed at higher levels and it's United Kingdom and Portugal.

And then in summary, kind of just a policy and reactions to the BSE occurrence and where the U.S. is going, the USDA anyway, again just a summary, our evaluation is based on the OIE criteria. The EU conducted its own geographical BSE risk assessment. They are to finalize their reports coming up. They have invited all the countries that they have evaluated now on these prelim reports to comment back and to comment basically on consistency between the countries. Were the reports consistent from one country to another? Did they evaluate you in the same kind of ruler or yard stick so to say? And the methodology, was it a fair methodology? And again, I think if you're outside Europe, some of the comments from countries outside of Europe that it was basically done with a lot of emphasis on system prevention and not import prevention. So that's one

thing some of the countries outside of Europe have made that kind of judgment.

So once Europe finalizes its reports, the U.S., we plan to reevaluate our classifications just to see we weren't out of line with the countries and then the status of the countries will depend on the prevention measures that are in place and have been in place historically, mitigation factors and again that there is this ongoing active surveillance to assure that BSE has not entered the countries.

A lot of this depends on BSE and a long incubation that what you've done, you know, eight, 10 years ago is important or four or five years ago is very, very important to your status, you know, presently. So if you take action today, you won't see results and I think you've seen that all along the way. Thank you. Do you want questions now or no.

DR. BROWN: Thank you, Linda. And we finish the morning's presentations with a presentation by Dr. Lower focusing now more on blood and he'll talk about new-variant CJD and blood safety in the European Union and potential human exposure to BSE and national and European community

surveillance activities and public policies concerning blood.

DR. LOWER: Thank you very much for the invitation.

I think there is a need to introduce shortly the relevant organization of the European Commission and to clarify my affiliation as mentioned in the Agenda, is that I belong and am representing DG XXIV, Consumer Policy and Consumer Health Protection which may be derived from a presentation I gave last September also here during a CBER meeting.

But in the meantime, the European Commission changed. It has a new president and he also reorganized the Directorate General. The correct name of the Directorate in which I am involved and a question we have to discuss today, next slide please, is now called DG enterprise and DG Health and Consumer Protection. So it means it's Roman numbers at top and you have short names. The abbreviation for Health and Consumer Protection is SANCO. There is not only the topping of Roman numbers but also a rearrangement of responsibilities and the DG Health and Consumer Protection is now also responsible for regulations on the area of

labeled blood products which was formally another Directorate General.

One of the tasks of the DG Health and Consumer Protection is to host a number of scientific committees, next slide please, which are listed here and the committee which has to deal with CJD and blood is the Scientific Committee on Medicinal Products and Medical Devices. Next slide.

This committee had a subgroup which has discussed to some extent the question of CJD and blood and this is the composition of this subgroup. You see there's also a representative of the American continent, Bob Rohwer and myself, I have chaired this subgroup. I think it's necessary for clarification to state here that I am not here in the capacity as a representative of the European Union. I do not speak on behalf of the European Union. I am a member of the Scientific Committee and I will explain to you the proposals and opinions of the Scientific Committee and I can also explain to you the general policy in the European Union but this is not, and I would like to repeat it, an official presentation of the European Commission here.

This group has issued two different

opinions, next slide. It shows the first, the name of the first, the title of the first, "Opinion on The Risk Quantification for CJD Transmission Via Substances of Human Organ" issued or adopted in October 1998, and we have developed recently an updated opinion, next slide, which was issued in February this year. You can get these opinions from the Internet.

I would like to review shortly the older opinion too before I go to the latest one. Next slide.

I just want to go through the main elements of the first opinion and this opinion deals with the question of the probability of CJD being or could be transmitted by blood and this is just to remind you that there are a number of epidemiological studies looking whether there's a higher risk for blood transfusion for example in CJD cases and none of these studies showed an increased risk for blood or blood products.

Next slide shows you the outline of many experiments which have been performed to check experimentally sensitivity in animals. Next slide.

There are a whole range of caveats which has to be discussed before extrapolations can made

from elemental experiments. I don't want to go through all of these caveats but most of them have been discussed in the opinion. Next slide.

Now I would like to show you just to remind you how or how less consistent the results are, a few figures. First of all there are no studies which reflect the human situation, namely that naturally infected animals are studied by testing the infectivity in the same species. That's true. There are no published studies. So far as I know, there is one study under way in the UK. There are blood or blood clots from clinically ill cattle injected into cattle. So far there's no positive outcome. That means there's no disease, but it's still too early to make firm conclusion. Next slide.

The next slide is to remind you that there is a study which comes very close to this situation, that is a study in cattle, which has been orally infected. This is as I would say very close to the natural situation. In this case, different tissues including buffy coat for example are tested in mice and you have to have the species barrier in mind and so far also there is not infectivity found in the peripheral blood of all the infected cattle.

Next slide.

There's a huge amount of studies which look for infectivity in animals using artificially infected animals in the same species as in the cattle animals but I show you a few pictures just to show that there in my opinion really a lack of consistency between all these studies. This for example is a study in goats. The goats have been tested in indicator goats and previously was not possible to find any infectivity in blood.

Next slide shows the first example of two studies which seem to be comparable as they use the same procedure to purify the infectivity frankly which is called P250s which were both done in hamsters and please look at this picture where Diringer Deerinch apparently found some infectivity in blood and infectivity in brain.

The next slide is a similar study by Mauricio Pocchiari in Italy and you get a completely different picture. Here he has a decrease in the infectivity in blood and in this case, spleen parallels very much high the infectivity in brain. Please also have in mind the correlation between blood and spleen and this comes to the question whether infectivity in the lymphoid organs reflects

infectivity in the peripheral blood and from this data you will not have the impression that there's parallel between infectivity in spleen or in blood.

Next slide shows studies from Manuelidis which he was able to found sometimes irregularly infectivity in blood of guinea pigs which had been infected with a CJD strain.

The next slide is the slide of the Kuroda model in mice where there is a clear increase in the infectivity in blood. At this stage I have to say these are not titers. These are the incubation period because there is no straight correlation between incubation period and titer. This is a huge over estimation of the infectivity in blood in these figures. I should ask I guess Paul Brown to give me the figures for titers to have a better graph to show the correlation between infectivity in blood and spleen. And again here there is no parallel lesson between spleen and blood. Next slide.

The conclusion from all these considerations from the interpretation of the experimental data is that there is no infectivity in blood of Kuru and CJD patients. However, I didn't show the pictures. The question is whether there is

an infectivity in iatrogenic CJD. There is only one study I am aware of and again the question is there infectivity in variant CJD and whether one should use transgenic mice. I think these experiments are underway, but to my knowledge, there is no data at least available to me.

What can be concluded from the studies in animal models, especially in rodents, is that there might be a low titer of infectivity in blood especially in rodents, mice and hamsters but this titer is very low especially if you compare these titers with the titers of viruses which are well known to be transmitted by blood. For example, HIV, HCV, HBV which have always titers over 10 to the 5th. This is 10,000 times more than the titer of infectivity in these rodents for TSE.

And another conclusion is here the question was a TSE agent can be correlated with or the infectivity can be correlated with peripheral leukocytes. As I mentioned, there is no parallelism between infectivity in spleen and blood. Next slide.

Now what we have to do to compare the experience with CJD and variant CJD, the CJD says no epidemiological evidence for transmission by blood

and the data with variant CJD are insufficient so far just because of the short time we are dealing with this disease and you remember the data presented this morning by Bob Will that there are no indications that infectivity can be transmitted or has been transmitted from vCJD cases. Always a problem is, of course, extrapolation of animal to the human situation but CJD, the prion protein, the pathologic prion protein is usually not found in peripheral tissues especially not in lymphatic tissue in contrast. These prions are found in the peripheral lympho-reticular tissue in vCJD cases and then the question is whether this makes vCJD more closely related to the animals' data and the question is whether the extrapolation from animal data for vCJD may be closer to reality than for CJD. Next slide.

A clear difference between CJD and vCJD of course is occurrence. CJD occurs all over the world with a certain unchanged frequency and in contrast vCJD is predominantly found in the UK and as we heard this morning, 57 cases are confirmed so far and 13 are probable. So there's no question that the risk for variant CJD is highest in the UK and residence in UK is thought as a risk factor for

CJD. And for this understanding USA, Canada and others have recommended to exclude donors who stayed cumulatively at least six months in UK between 1980 and 1996. Next slide.

I would like to show you the next three slides shortly what the reaction in Germany was. First again the organization of German. The Ministry of Health is advised by what we call Arbeitskreis Blut which could be translated as Blood Advisory Board and it supervises also the Paul-Ehrlich-Institut. I'm Acting Director of this institute and our duty is to license plasma derived products as well as label blood components, perform batch control, possible hemovigilance.

This Blood Advisory Board discussed I guess in August or September last year some measures introduced by FDA and it's similar to the situation in your Advisory Committee here to have been asked a number of questions and voted on this question. I would like to show you the results of this voting. Next slide.

The first question was there are no new scientific data which may change the risk assessment regarding the transmission of vCJD by blood and from the 29 members, 28 said yes and one abstention. The

next point was FDA measures cannot be transferred to Germany because of differences in basic assumptions. There was a unanimous no to this possible transfer of these measures to Germany. Next slide.

The next question was whether a survey of blood donors regarding their pattern of travels to UK should be performed, and there was a very close outcome as you see, 14 no and 13 yes, and then there was a question which was also raised in other countries which was not openly discussed here, namely whether UK citizens should be excluded from donations. That means that the British passport would be a surrogate marker for residence in the UK and to this question there were nine yes and 11 nos. So it was rejected. That's still the official situation in Germany. There is no decision. Three is one deviation from these votes of the Advisory Board, namely that there is intended to perform a survey on the travel patterns of the blood donors. Next slide.

So I think there are a number of questions especially in Europe which are connected with the measures introduced here by FDA and the Canadian health authorities. The basic question is does the exclusion of donor who stayed for some time

in UK really contribute to the safety of the blood supply? And then you have to take into consideration what is the risk to acquire the variant CJD in the EU outside of the UK? And, of course, how does the exclusion of donors influence the blood supply quantitatively and qualitatively? Next slide.

What is the risk to acquire vCJD in the EU outside UK and this is an issue we have already discussed. You know, you have seen figures have substantial export of live cattle from UK to Europe especially to France and Netherlands and again the question is what is free exportation from these countries? I could easily mention, for example, that some of these materials is exported from Netherlands and France to Germany and this is not only true for live cattle, but also for bovine material and we have discussed it although here today there is still indigenous BSE in continental Europe especially Portugal, Switzerland, France and so on.

I again have included a chart of the occurrence of BSE, next slide, in all the other member states taken from the figures published by the Office International des Epizootics. You can

see the increase for example in Portugal and I have to again stress as Bob Will has done that these are very low figures compared to the occurrence of BSE in the United Kingdom.

What I would like to mention is a fact that was already covered by Dr. Heim, namely the increase of BSE cases in Switzerland which was due to the introduction of test for the presence of BSE, not just clinical observation but indeed testing and this shows to me in this case you have an increase of at least by 100 percent and this means to me that also in the other countries unrecognized cases of BSE come to the slaughter houses. And the question was raised here in which countries in Europe the specified risk material is removed from the cattle during slaughtering, I have not a complete list I have to say. I know as mentioned it's done in the UK, in France, in Switzerland. It's also done in Portugal to my knowledge, but I have no idea whether it's done in Netherlands or Belgium and it's for sure not performed in Germany.

So in my opinion there is still a procedural risk of infection of European citizens by BSE containing material. This risk seems to be very low compared to the risk in the United Kingdom, but

there is a certain procedural risk. Next slide.

This risk is exemplified, of course, by the vCJD cases outside of the UK and we have already discussed here and have written here a more provocative question, namely what is the relative risk of many people staying 60 months, that is five years or 600 months, this is 50 years, in Germany, France or Portugal versus a small percentage staying six months or longer in UK? I guess the answer to this question is very well shown in the study performed in France which came to the conclusion that the indigenous risk in France is much higher than the risk by traveling to UK. Next slide.

On the other hand, if one assumes that the risk outside of the UK is close to zero, as I guess U.S. may judge, then of course would be meaningful to defer all people who visited the high risk areas. A practical problem seems to me and this is the question you have to answer if I understand it correctly today, whether measures can be extended if you have once decided to exclude let's say visitors to a certain country, how difficult is it to extend it, and the question will be especially with Europe, you have in my opinion residual risk, how to set the cutoff, where you

should stop it, where can you stop or when or where you have to continue. Next slide.

The first point, I will come back a little later, but I want to mention here, of course, is also that if you exclude donors, you have to replace them by first time donors and it's well known that first time donors have an increased risk for blood-borne infections especially HIV, HBV and HCV.

The next slide says the real question to me. How many HIV infections are we ready to accept in exchange to the reduction of the risk from exposure to BSE in UK? HIV infections are a real risk in my opinion. The other one is still a theoretical risk and I know it's difficult to calculate the risk, but I've taken from the French study that there is an estimate, a reduction or a deferral of donors who stay in the UK according to FDA who will both create at least one additional HIV infection per three years. So that is indeed a real risk but this data, I admit are difficult to calculate and it may be possible for HIV, but it's more difficult to calculate for HBV and even HCV, but one should have it in mind that deferral of donors because of their travel to the UK creates

adverse effects in the sense that you have an increase in transmission of other viruses. Next slide.

So the SCMPMD, Scientific Committee for Medicinal Products and Medical Devices, came to the following conclusion in its opinion of February 2000, is that before we make any decision or any recommendation, we need more data. First of all, we should know the travel pattern of European donors which may differ between member states. Next slide.

The next slide is a first attempt to draw as a graph data we have already seen, namely the cumulative risk coming from travel to the UK and this reflects as it was already explained to us, different travel behavior in USA and in France. You have to look at it from this side. It means if you exclude all people who stayed for more than five years in the UK, you have a reduction of the risk by around 30 percent in France and even more than 50 percent in the U.S. So if you, for example, exclude all persons who stayed more than six months, you came up with a reduction of the theoretical risk by around 90 percent in the U.S. and only by 70 percent in France. Next slide.

What I also want to mention here is, of

course, you will have different curves for different countries in Europe. So I would imagine for example in Ireland you will have still steeper curve meaning that there are more people staying for short time in the UK, one day travel to the UK and, of course, in Greece for example, I expect the curve would be much closer to the U.S. Then we have, of course, the problem in Europe if you want to defer travel as to UK, on what basis. Should we have the same reduction in theoretical risk. Then we have to do it according to this straight line, that means if you use reduce the risk in the U.S. by around 90 percent, you have to exclude in France for example all donors who stayed for more than one month in UK. I expect for Ireland that you need even to exclude people who stayed for short time, increase for example maybe closer to the U.S. situation but this would mean we would have very different rules all over Europe in different countries to have the same reduction in theoretical risk. On the other hand, one could say very easily exclude everybody who stayed for six months or longer in the UK, but then you have different outcomes in the different countries and Dr. Asher mentioned that there should be no discrimination. It would be difficult in

Europe to discriminate between French people who stayed shorter time in UK and people who stayed for longer time in the UK. So what I want to say here, it's very difficult for Europe to make a consistent and scientific based decision on the dates if the decision would be to exclude donors who stayed in the UK. Next slide.

The next issue is the SCMPMD asks for exposure to UK bovine derived material, also for the other member states and also for the prevalence of HIV, HBV and HCV in first time donors, and only if you have all of this data, you can perform a scientifically based judgment on the effect of the deferral of donors, and I think a very excellent study has been performed in France and I hope that similar studies will also be done in the other European countries, but my impression at the moment is that there is not a great enthusiasm in Europe to perform these studies at least questionnaire for, just to ask for travel pattern which has to be finalized by the European Commission has not yet ensued to my knowledge at least although it was drafted end of last year. Next slide.

So the summary on donor deferral, there's no decision in the EU so far. The survey is

initiated but not yet been performed. There are a number of groups which try to get the European harmonization. I will not stop at this place because I think these discussion urged the European authorities to think about other measures to reduce the theoretical risk of vCJD transmission because there would be pressure by the public if European authorities would not decide to exclude the donors who stay for some time in the UK, and therefore this discussion has to be collected, namely the discussion of leukofiltration which is the theme of tomorrow. Next slide.

So the SCMPMD also gave its opinion of the leukofiltration and the conclusion is maybe is that the extrapolation from animal models with a peripheral distribution of the prion protein has been found, and also infectivity in blood, that this infectivity is mainly associated with the cellular components or the white cells of the blood. This may be extrapolated to variant CJD. Next slide.

And therefore leukofiltration could be helpful, but there are, of course, many caveats and I guess they will all be discussed tomorrow. There's lack of experimental proof of reduction of TSE infectivity. Nobody knows exactly which cell

types carry TSE infectivity in the white blood cell compartment. Nobody knows to what degree these cells are removed by filtration. Nobody knows what effects the different types of filters have. There's lack of validation and there's an urgent need definitely to study all these questions. But one has to realize that answers to these questions will only be available if studies are started immediately, the answers will be available maybe in two years from now. Next slide.

Therefore the SCMPMD said in the meantime until this data is available, it might be advisable to introduce leukofiltration as a precautionary step emphasizing the Precautionary Principle which was mentioned already by David Asher in his first talk. A recommendation for the general use of leukofiltration would be in line with the belief that many, if not all transfusion recipients would benefit from the removal of white blood cells for other reasons.

This is just in contrast to the deferral of donors. If you introduce leukofiltration, you do not really know what the effect will be but it will not cause, it will not have a negative effect. It has definitely a positive effect unless somebody can

show that leukofiltration can enhance infectivity in blood but I have only heard rumors about it and haven't seen any data.

I would like to close with a short experience I recently had. We in Germany do not perform leukofiltration. So far you have heard it's introduced in France, in Switzerland, but I had proposed to introduce it, but one argument, of course, are the high costs for leukofiltration. We had a short meeting with our Minister of Health and after a short time, I learned that these costs are not in the range a minister really cares. These are tens of millions of deutsche marks. He has other problems with billions of marks with the health care system. So the money which is needed for leukofiltration doesn't count at least in Germany and we have also our problem with the healthcare budget. Thank you very much for you attention.

DR. BROWN: Thank you, Dr. Lower. Before we begin the questions and discussions, it was pointed out to me that perhaps not all members of the Committee are familiar with some of the abbreviations that have been used or even some of the terms that haven't been abbreviated. One such term was specified offal and, Bob, I think, Dr.

Will, are you in a position to tell us in the UK what is meant by specified or just offal, specified bovine offal, SBO, what tissues?

DR. WILL: I think the major tissues are brain, spinal cords, spleen, and intestine are the main ones.

DR. BROWN: Does it include all viscera, at least abdominal viscera?

DR. WILL: The whole head is now a specified risk material as well.

DR. BROWN: Right. Certainly the central nervous system and the head.

DR. WILL: Yeah.

DR. BROWN: All abdominal viscera.

DR. WILL: No, spleen and intestine.

DR. BROWN: Spleen, intestine.

DR. DETWILER: The spinal column.

DR. BROWN: Yeah, sure. What about the chest cavity, lung?

DR. DETWILER: Thymus but not lung.

DR. BROWN: So head, spinal cord, thymus, spleen and intestine. Anything else?

DR. WILL: Eyes.

DR. BROWN: That's the head, okay. That's gone. Anything else? Going, going, gone.

Annick, did you -- someone over here had their hand up?

UNIDENTIFIED SPEAKER: Tonsils.

DR. BROWN: Is that true for the UK? Because one of the questions -- that's the head as well. Anything that's in the head? Brain, eyes, tonsils.

DR. DETWILER: No, I believe the UK the tongue is excluded. Is that not correct, Bob? It's excluded.

DR. BROWN: Okay. And again so that's in the head. Once you take the head off --

DR. DETWILER: No, the tongue is excluded.

DR. BROWN: Oh, I see. You can cut the tongue out and then you throw the rest of the head away, okay. Now the follow up question on that is -- yeah, Ernie.

DR. BELAY: What about the bones? The UK had a ban on beef on the bone.

DR. BROWN: Yeah, but I don't think bone is a specified offal, is it, Bob?

DR. WILL: No. What happened was that there was an experimental result that showed there was infectivity in dorsal root ganglia.

DR. BROWN: Right.

DR. WILL: Therefore there was a ban on the use of beef on the bone.

DR. BROWN: Right.

DR. WILL: That was present for some years but was withdrawn later last year. So it is now again legal to use beef on the bone.

DR. BROWN: Okay. So in the United Kingdom, the head is removed, the vertebral column is removed, the tongue is usable as the only entity from the head, and the thymus, spleen, intestines are also excluded, that is they are specified offal. So the next question is, is the definition of specified offal similar or not similar, identical in every European country? Yes.

DR. LOWER: As I have mentioned not every European country removes the specified risk material. What I would like to do is to remove these tissues from the proposal of the Commission of decision which should be coming forth in the next few weeks or months, and I can explain exactly what is meant with specified risk material that should be removed.

DR. BROWN: Just to be so that the Committee is clear, this is proposed, not in effect

now.

DR. LOWER: This is proposed and reflects, of course, the practice in such countries which remove the specified risk material.

DR. BROWN: Right. Can I first interject is at the moment, as we speak, is there any other country in Europe which has implemented a policy of removing specified bovine offal from its cattle? I assume Switzerland has --

DR. LOWER: Yes.

DR. BROWN: -- because we heard from Switzerland. Are there any other countries? France or all.

DR. LOWER: Yeah, and Portugal also, yeah. And Ireland also, yeah.

DR. SCHONBERGER: I think Linda did a survey on that. Maybe she can --

DR. BROWN: Yeah.

DR. DETWILER: Actually that's in the GBR. The countries that have --

DR. BROWN: What's a GBR?

DR. DETWILER: The Geographical BSE Risk Assessment.

DR. BROWN: Okay.

DR. DETWILER: Okay. It's probably

easier to say the countries that have not.

DR. BROWN: Okay.

DR. DETWILER: The countries that have no SRM, specified risk material bans are the countries that have not confirmed BSE. So like in Category III it would be Germany, Spain and Italy and then Finland does not, Sweden does not, Norway does not, and all the others --

DR. LOWER: Netherlands and Belgium also do.

DR. DETWILER: Netherlands and Belgium have them but they've confirmed BSE.

DR. BROWN: It occurs to me that -- let's just take Germany since we have Dr. Lower at the microphone and, Linda, you said that Germany falls within the category of BSE likely but unconfirmed. In other words, it's I think in the four categories, it's the third category which is next to the fourth category.

DR. LOWER: But is also close to the second and U.S., and Dr. Detwiler didn't mention in European categorization US is in the second category.

DR. BROWN: The U.S.

DR. LOWER: Yeah.

DR. BROWN: The U.S. is in the second category.

DR. LOWER: Yes.

DR. BROWN: In any case, the third category by definition is likely BSE but not confirmed.

DR. LOWER: Right.

DR. BROWN: I had a question that relates to sort of both of these questions. What constitutes likely but unconfirmed? And the second part of it is it's curious to me that a country in which BSE was likely but unconfirmed should not take any action with respect to specified risk materials?

DR. LOWER: If I should answer, the Scientific Committee who evaluated that there could be a BSE risk, took into account also challenges for the system. There's what they call the stability of the system. Challenges importation of cattle material for example and stability means if I remember correctly, that these things are published just two days ago, it includes the surveillance for example, the extent of the surveillance and also the order of measures taken in the different countries and taken together, all the challenge and the possibility to detect BSE lets the commission come

to the conclusion that there is a likelihood for presence of BSE in Germany and some other countries. Also it has not been confirmed today. This is an augmentation of the BSE scope.

DR. BROWN: Yeah. Any other questions? I don't want to enter a dialogue. I'm a little surprised that the U.S. should be Category II, that is to say unlikely but --

DR. LOWER: But excluded.

DR. BROWN: -- but not proven, yeah. I mean why -- what do you need? Why should the U.S. differ from Norway in this respect?

DR. DETWILER: Let me -- I might as well go over all the countries since this came up here and I probably should have. It would have been easier.

In Category I were Norway, New Zealand, Argentina and Paraguay, and basically the cutoff was in order to try and keep it consistent again, Norway had that little caveat now because of the trade with Denmark, okay, but if you imported less than 20 cattle from the UK prior to 1988, that's how you got in a Category I regardless of the stability of your system. So those countries like Paraguay had no trade with the UK, all right, and that's how. New

Zealand had less than 20, Argentina had less than 20 and Norway had a small number. So basically that's Category I was regardless really on the stability of the system.

DR. BROWN: Is there some magic about the number 20?

DR. DETWILER: It was done on an assumed prevalence or incidence in the highest or after '88. Again it was hard to come up with these numbers but the best way is to go on the web page and read the whole procedure in how this was determined because it's complicated.

In Category II were, let me go through so I don't miss anybody, Australia, Austria, Finland, Sweden, Canada, Chile, Czechoslovakia, the Slovak Republic and the U.S. Again these are countries that submitted.

Category III, you saw the entire list because there is no country other than European countries that were in Category III, and Category IV were only the UK and Portugal.

One of the things I think that concerned from U.S. perspective on SRM, and maybe to take into consideration considering this, is that because again trade within the European Union, France can

have a ban in place, Switzerland is different because they're not a member state, but if cattle can be born in France, move to another country to be slaughtered, moved to yet another country to be processed, and depending on the regs in the country, may or may not have SRM removed, okay, then that finished product can then move throughout the European Union. Okay. So you can see how it gets really complicated trying to separate out countries because of trading practices.

DR. BROWN: Yeah. We'll have some Committee questions now. I think the sense of whatever you've heard in the last five minutes is that the Committee is going to have a great deal of trouble basing any of their decisions on the present categorization of specified risk material policies in the various countries which seem to me still to be work in progress. Yes, we have a question from Blaine I think.

DR. HOLLINGER: I just want to ask Linda again, does that mean that cattle could be moved from Britain to France and then be moved from France to another country also?

DR. DETWILER: I'm sorry. I'm glad you pointed that out. There are certain countries that

have exclusions on them to send cattle and right now United Kingdom and Portugal, correct? Portugal. Yeah. They are the two that you cannot send out by EU regulations. Okay.

DR. HOLLINGER: This is now or was it 10 years ago?

DR. DETWILER: It started in the full, for all ages was '96, right? How about breeding? The breeding animals or the older animals that were in the earlier nineties, 1990, and then all ages was 1996 for UK and then Portugal I believe it was '98.

DR. HOLLINGER: And what kind of products are usually sent from say UK to France? Are these processed meats primarily? And is it products, various types of products that were sent there or what?

DR. BROWN: Bob.

DR. WILL: If I could just answer that question it comes back to a point that was made earlier. One of the problems with calculating exposures in other countries and in the UK is you can do it based on things like the instance of BSE but, of course, that's very much an indirect mark of human exposure. What you really need to know is what SRMs went into the human food chain? What were

the inclusion rates? Did they vary with time? Were those products exported to other countries, et cetera, et cetera? And we do not have that information. Even in the UK we cannot tell accurately what the actual exposure was and therefore trying to derive exposures in other countries based on this is virtually impossible in my personal opinion although I'd be very open to other people's views about this. The issue of exposure based on BSE itself is one issue, but actually going from that to actual human risk is a very difficult issue.

DR. BROWN: Question.

DR. SAYERS: Yes, I've just got a comment and a question for Dr. Lower. I think the opportunity to discuss the categorization of various countries is really only a temporary luxury. If prior related disease has done anything, it's reminded us thanks to international trade in livestock, international trade in meat products and international tourism, that we really are just a global village and the United States is as much a suburb of that global village as is Norway. So much for that comment.

A question for Dr. Lower. You pointed

out to us that there is in fact a tradeoff and in return for trying to prevent something which has not happened, namely deferring UK donors, the tradeoff is introducing into the blood supply individuals who are first time donors who have an increased risk for HIV, HCV, Hepatitis B, and I'm wondering if it isn't worthwhile including in that enhanced risk with the deferral of these potentially risky UK donors where they're including in that calculation the risk of CMV in those first time donors? And the reason I ask that is an increasing number of transfusion recipients are immuno-compromised these days and they're at risk at transfusion of CMV and we know that neither leukoreduction nor serological screening of donors for CMV is 100 percent effective in reducing the risk of transfusion transmitted CMV.

DR. LOWER: I think HIV, HCV and HBV are lead examples of viruses which are really transmitted by blood. One, of course, can include CMV. I have no idea how feasible it is to calculate the increase in the risk for CMV. That's a question to an epidemiologist maybe.

DR. BROWN: Yes. I'm sorry. I'm asleep at the switch here. Paul.

DR. McCURDY: I'd like to comment on

that discussion about donors. In the first place, there's no rule that says you have to replace a donor that's deferred with a first time donor. The mean number of donations per donor in the United States is 1.6 or 1.7 which is exactly the same figure that's been around since the middle seventies. So that if you can get those donors to donate one more time a year or certainly a reasonable number, then you can make up virtually any shortfall that you want to make.

The other thing is that the prevalence of disease markers in first time donors is clearly higher. There have been a few attempts, one of which is in the NHLBI REDS Study, to look at incidence of infections in first time versus repeat donors and the data admittedly is a little difficult to figure that out sometimes, but the data would suggest that first time donors are essentially the same as repeat donors when you look at incidence and the incident infections are the ones that are going to be transmitted, not the prevalent ones.

DR. HOEL: I have a question for Dr. Will. You had mentioned that the dietary habits had been looked at and it was controversial with the epidemiologist and what I'd like to know is have

they looked at the prevalence of particular meat products that are consumed by the older individuals in the UK compared to purportedly what these cases said they took or the prevalence within that age group?

DR. WILL: One of the problems with this is that you really want to have surveys of eating habits in the 1980s to determine what the risk was and there have been some household surveys done, some limited information is available, but it's across a broad age range including adults up to I think the age of over 60 and so obtaining information directly on the correct age, there is some information available and Sheila Gore, our statistician had said that she feels that this may correlate with the age distribution of variant CJD. However, as I said the exposures are still uncertain, and the most important exposures in terms of which food products are uncertain also. We are carrying out a case control study to try and determine with age and sex match control whether there is an increased frequency of consumption of a particular product in the cases of variant CJD and as of yet have not come to any definite answer there. One of the problems with this study and

there are many of them methodologically is the fact that we cannot target the questionnaire onto specific products that we think would be at greatest risk. So the question is a very important one, but I think currently it's difficult to give you a very accurate answer.

DR. HOEL: I see. Because too much time has passed basically to retrospectively go back and get those dietary habits from the elderly I'm guessing.

DR. WILL: Well, I think you can look. I mean you can get some feeling but there may be some different dietary exposures in different age groups, that is true, and it's intuitively correct as well, but the problem is that the epidemiologist, for example, Peter Smith, is unhappy if that's an explanation for the age distribution of variant CJD because of the very wide age range of individuals who have been affected by this condition.

DR. BROWN: Yes, Peter.

DR. LURIE: It seems to me that this debate is going to come down the way it did, the lost time in the sense that we're going to be balancing the same kinds of things against one another. This afternoon we'll hear about the risk

to the blood supply, and this morning it's all about the exposure in effect, exposure versus risk.

Now Don made the point that the ideal thing that we like to look at is the number of animals in effect who slip through the existing screening systems and the point seems to be that we can't really make those calculations anywhere outside of Britain and a surrogate for that might be the kinds of things that Dr. Will was talking about which is not only looking at exposure rates in terms of infected cows but rather looking at the particular bans that were in effect at the particular times and how that might give us some sense of what actually enters the food supply, but as he pointed out, that's difficult to do in Britain and probably more difficult still to do elsewhere. So that's not going to work.

So it seems to me that at least for this morning's part of the discussion, most of it comes down to is what is the rate of BSE per say million cattle between different countries? That seems to me in effect what this really comes down to. And unfortunately most of the presentations this morning, not all, but most have focused on the number of cases of BSE and don't have denominator

data with the exceptions of the data presented by Dr. Ducrot and later reiterated by Dr. Detwiler. But what we have really is comparative incidence data only for 1998 and 1999 and what I'm interested in is really in the trends of those rates over time dating back to some period like 1980 and how those compare to the British rates over time going back to say 1980 and the data that we have on Britain unfortunately lumped together the first seven or so years of the time where, you know, after the first cases of BSE were identified.

The difference between these unavailable data and the other unavailable data as suggested by Don and Dr. Will, these actually could exist and I find it a little frustrating. To me that's important data that could easily be calculated and put on a slide, but somehow we seem to be lacking that and I'm wondering if there's some way of putting that together.

DR. BROWN: Linda.

DR. DETWILER: Boy, to say that they're easily calculated, I would totally disagree with that because you're talking all those numbers up there, okay, except for probably Switzerland is probably closest to being accurate. They're not

easily available because first of all you just have reported cases and you heard from Dr. Heim that that really is dependent upon a lot of factors within the country. So all you would have are reported cases and you'd have to figure in factors of surveillance system and what was going on at the time, and that's it. So I don't think you'd get an accurate number at all of the surveillance in countries even if you could try and figure out because you'd just be guesstimating what was influencing what country at what time. So, you know, the first case outside of UK was in 1989, and then you have countries come on board and you saw the Benelux countries in 1997. So I think until the EU puts in place the targeted surveillance, I don't think any of us are going to have any decent idea of what's really going on in the cattle population and again I don't know if you can try and go back and you might be able to do some calculations back. A lot of people have tried to figure that out with no success.

DR. LURIE: I'm not saying anything really that complicated. I mean you're clearly right, that different surveillance systems will produce different numbers in the data from Switzerland and the increases in recent years show

that. I think that's clear, but nonetheless, the fact that there are difficulties interpreting the data doesn't mean that you should not look at the data, and all I'm really saying is were the number of BSE confirmed cases in cattle through whatever your surveillance system is, divide that by the number of cattle that existed in that particular country at that moment in time, and what are the trends? Then we can go about adding caveats of the kind that you're talking, but I don't think it's an excuse not to look at the data.

DR. BROWN: If I could interpose a -- go ahead, Susan.

DR. LEITMAN: Go ahead.

DR. BROWN: I'm guessing that it's not going to be possible, it's more than a guess, it's a certitude, it will not be possible for this Committee today to judge risk to the blood supply from residence in a foreign country on the basis of present data with respect to the number of cattle with BSE in that country. I will be taking myself a very simpleminded approach to this in view of the uncertainty about the amount of indigenous BSE in any given European country and all of the things that intervene between the number of cases of BSE in

a given country and the risk of new-variant CJD in a given country and then the further risk of blood from such a population being a risk factor.

I'm likely to go back just to the phenomenon of new-variant CJD in the United Kingdom which was the main consideration in the previous meeting and the new data coming from France and we will get into that later this afternoon, but certainly we can't, it's putting too fine a point on equating what we're supposed to do which is risk to blood from people in this country who have visited countries that have BSE, for example, BSE without new-variant CJD. I sense that the Committee is simply not going to have data available as you point out as everybody is aware of to make this determination on the basis of BSE identified in various countries. So as I say, we're going to be more focused on the actual closer to humans and blood this afternoon and we'll get on with it then, but, Larry, do you have something to say?

DR. SCHONBERGER: Yeah. I think I tend to agree with you, Paul. It may be useful though in this setting to get some comments confirming that the surveillance at least for humans is pretty consistent throughout Europe including particularly

Portugal I guess where they're saying that BSE, that's classified as a Group IV country. Can we assume that Portugal has a reasonably good surveillance for the human disease as Paul has indicated?

DR. BROWN: Yeah, I think that's good. Perhaps Bob might be in the best position as the sort of monitor of European wide CJD.

DR. WILL: Well, now I think as I've said a system has been set up in which we try and harmonize the methodologies of surveillance and the case definition. We've also tried to improve diagnosis in various countries particularly with the use of 14-3-3 immunoassay and that is an important source of referral in identification of cases and such systems have been set up and I think now all countries are participating in the system and workshops have been held to try and improve these available methodologies in countries taking part of the system.

Having said that, of course, not all the countries have the same type of health care system, and not all the countries have the same resources for doing surveillance. And therefore I think there may be some variation in how effective the

surveillance works and one final thing I would say is that it is very easy for a country that has experienced surveillance for many years to continue doing the surveillance. It's quite difficult to set it up in the first place, but I do think that we're trying very hard to insure that everything can be done through the European grant to insure that surveillance systems are in place in all countries and my own expectation is that I think it is quite likely that cases of variant CJD will be identified in participating countries.

DR. SCHONBERGER: Well, maybe one way to get a handle on that is to ask maybe how many cases of the sporadic CJD that countries have identified and see if it's within what you might expect, you know.

DR. BROWN: The European surveillance is pretty good in this regard, and Bob certainly has information about the trends of sporadic CJD or non-new-variant CJD to put it globally and virtually every country that's participating.

DR. WILL: I think in the main countries that have been carrying out surveillance for some years, the incidence rates are now I think in all these countries over one case per million per year

and relatively comparable in all countries. I think with some of the countries that have started surveillance, that is not the case, and I think it does take time to establish a surveillance system that is effective and as I say, it depends on resources also but certain countries having had a relatively low incidence of CJD, of sporadic CJD, now have a higher incidence. For example, Spain and it took a few years for them to reach that stage, and I think that no one can expect a country to start doing surveillance and have highly efficient surveillance within a very short period. It does take time and I think that we are trying to help as a group to try and improve surveillance in country who only recently started doing this. So I think in the main countries the comparable rates for sporadic CJD as you mentioned I think they are comparable but I think that's not necessarily true for all contributing countries at the moment.

DR. BROWN: Yeah. I'm going to ask Jay to give his comment, but just to be specific and concrete, for example, Germany and France certainly have, and the UK, have had surveillance systems in place for many years and their surveillance systems are exceptionally good and they've all reached

roughly the same plateau of CJD incidence, but again to be very concrete, Portugal which is one of the countries of great interest because of its apparent increase in BSE, we cannot yet say the same thing about either the surveillance of BSE or the surveillance of CJD. Jay.

DR. EPSTEIN: I agree generally with those observationst, but I just wonder whether at a cruder level we can't get a quantitative feel for relative risk and as a background, I'd like to suggest that any donor deferral policy as a precautionary measure has to be seen as only a partially effective measure. I mean no one expects that it could contain all risk, and in the end we need to think about what the marginal contribution of expanding deferrals.

And in that context the way I see things, there are two useful measures here of the relative risk. One is to ask, well, what proportion of new variant cases are outside the UK? And the available data suggests that it's only about five percent of all known cases. Even if there were one or two missed cases outside the UK, we'd still be to the same order of magnitude or relative risk. I think that those data at least at a superficial

level appear to correlate with risks from food exposure to affected animals in the case of France. What we heard if I understood it correct is that an analysis of consumption of beef from the UK suggests that from five to 10 percent of the beef in France would have been from the UK, and that that is in agreement to order of magnitude with the apparent case rate of new variant, suggesting that, you know, crude as it is, these numbers have some correlation.

Then moving to the question of whether the other BSE surveillance data are useful, I would frame the question this way. The reported case numbers for all the non-UK countries in each case are at most a few thousandths of a percent of the UK reports. If you look at all cumulative case reports, the highest one is in the Republic of Ireland, 454 compared to about 178, 179,000 in Uk. And the question that I would ask is could the countries that have had low number reports have missed epidemics ten or hundredfold higher because even if they were hundred fold higher, they would still only be 10 percent of UK, not looking at it as a rate per million cattle, but just looking at it as number of infected animals that could have potentially entered the food chain.

So I think it's possible to look at the crude data and get a little bit of a handle on the relative human risk. So what I'm suggesting is that even if there were under reporting of BSE and even if there were a few missed cases of new variant outside of the UK, are we not in a position to state that we think that the relative risk must still be in the domain of 10 percent or less? Because if we can conclude at least that much, it gives us a handle later in the day on estimating the potential utility of expanding a deferral strategy recognizing that it might only be a marginal added safety benefit. And that's just another way of looking at it.

In other words, I'm suggesting that it's not all one issue, that if you have a indigenous case, therefore you must have a deferral policy. It's a question of what's the benefit or precautionary benefit of the deferral policy as a whole, and I think there are some data on the relative risks both from the new variant case report and from the BSE report albeit in the fact of limited surveillance.

So the long and short of it is that I would ask that Dr. Detwiler, you know, do you think

that a hundredfold or greater BSE incidence could have been missed in any of these countries?

DR. DETWILER: Not a hundredfold. I think my vet colleagues from Europe will concur with that.

DR. BROWN: Yeah, we're going to break for lunch now.

DR. WILL: I wanted if you -- I did say I would answer Larry Schonberger's question. Do you want me to do so now or later?

DR. BROWN: It's been so long, I don't remember what the question is. I also had something. Yeah, go ahead, Bob. Answer whatever, whenever it was. Go ahead.

DR. WILL: Well, the one thing I apologize for being slightly imprecise this morning. My understanding as I recall is that the youngest, that the date of birth of the last case of BSE, the youngest case was in January '96 I think, and therefore it is likely that all the cases to answer Dr. Rohwer's point in 1999 were over 30 months.

In terms of the 30-month scheme and it's relative efficacy in protecting human health in relation to the SBO ban, historically in the UK the SBO or SRM ban was introduced in 1980. I personally

felt that was an absolutely critical measure to protect human health. The issue of using the over 30-month scheme in addition was introduced after the report of variant CJD on March 20, 1996, and was introduced by the UK government as an extra protective measure because of the understandable concern about public health in the UK. To introduce an over 30-month scheme in addition to an SRM ban, that might well increase further the protection of human health in countries with BSE, but as Dr. Asher said at the beginning, any measure that is taken on the Precautionary Principle should be proportional to the likely effect and cost and impact of such measure on other aspects of the country, and I think that therefore the issue of the over 30-month scheme in the UK is entirely understandable because of our position in relation to BSE and the situation in relation to the risk to public health. Whether such measure is appropriate in other countries I think is something they will have to consider individually.

DR. BROWN: Thanks, Bob. I'd like to give the Committee something to chew on for lunch. The beautiful thing about the French experience versus the UK experience is that the population of each country is roughly the same. Britain has had

about 60 cases over a period of -- total cases of new-variant. France for all intents and purposes had a total of three cases. If the imported consumable beef products to France is in fact five percent, then it works out beautifully even to people who don't like arithmetic. You've got 1/20 of the exposure in France. You've got 1/20 of the number of new-variant CJD cases.

If another country had instead of five percent let's say .5 percent and we used the same measure, then we could theoretically calculate what the risk might be. Maybe in three or four years there will be a case of new-variant.

So what the Committee is going to be faced with at some point this afternoon is saying, all right, we'll establish a deferral policy for France and perhaps it will be a year's residence or a year and a half residence, and then a policy for a country that doesn't yet have new-variant, and then we have someone in the blood bank with a calculator who asks the question, how long have you spent in the United Kingdom and the response is four months, but I spent a year and a half in France and six years in Germany. And so what's the combined risk? Does it go over or does it stay under? And

obviously I'm teasing a little bit. No one is ever going to be able to do this, but unfortunately one of the questions is going to address this very problem this afternoon.

We'll reconvene at 1:30. Yes. Reconvene here at 1:30. Thank you.

(Whereupon, the foregoing matter went off the record at 12:42 p.m. and went back on the record at 1:33 p.m.)

AFTERNOON SESSION

(1:33 p.m.)

DR. BROWN: Is Dr. Christopher Healey in the room? Dr. Healey? Is Kay Gregory in the room? You're Kay Gregory?

MS. GREGORY: Yes. Dr. Molloy is across the hall.

DR. BROWN: Beg pardon.

MS. GREGORY: Dr. Molloy is across the hall.

DR. BROWN: Who? I'm sorry. I can't hear you.

MS. GREGORY: Dr. Molloy is across the hall.

DR. BROWN: Okay. Are you Dr. Molloy?

UNIDENTIFIED PERSON: No.

DR. BROWN: You are not. Is Dr. Molloy here?

DR. MOLLOY: Here.

DR. BROWN: You're Dr. Molloy. I should have recognized you. Dr. McCullough, you had a question about the possibility of infectivity in TSE apart from central nervous system contaminated meat products.

DR. McCULLOUGH: Yes, I wondered if we

might be a brief comment on the implications of dairy cattle being infected with TSE and whether this has any implications for the infectivity of dairy products.

DR. BROWN: Dave, you might want to answer that. The question is what is the basis for a lack of concern with respect to dairy products since dairy products are the other major consumable for humans from livestock?

DR. ASHER: You will notice from Linda Detwiler's presentation that dairy products have never been considered a product other than minimal risk since the beginning of the TSE era, and insofar as I know, unlike the situation with blood, there all of the data are limited. No experimental studies to indicate that milk contains any detectible infectivity. The OIE, the European Commission as well as both the USDA and FDA in the past have expressed no concern about the safety of milk. That having been said, all these decisions always have to be considered interim and should any new data appear consistent with newly recognized risks for milk, it would have to be reevaluated.

DR. BROWN: Thank you. Is that satisfactory?

DR. McCULLOUGH: I just want to be clear. There is data, right, that shows no infectivity?

DR. ASHER: There are a limited number of studies. David Taylor did a study of BSE and, of course, for scrapie one can argue that we don't really know what the perinatal spread, the mechanism for the perinatal spread through milk is, but certainly a mammary gland study by Bill Hedlow years ago was negative, and I'm not aware of any study of milk although again they're limited and has indicated infection and I suppose the potential maternal calf spread until it's convincingly ruled out which hasn't been yet would allow the possibility for there having been a milk-borne spread, but there's a long regulatory history suggesting that milk is of no concern. Again all these decisions have to be considered interim and obviously there are some who have concern about any product coming from a diseases animal.

DR. BROWN: In short, there have been studies, all of them negative, in terms of detectible infectivity in milk and perhaps most appropriate or relevant, in two cases of Iatrogenic CJD in pregnant women, the women nursed their

children and their children continued to live in good health in one case 25 years after and second, milk from nursing mothers with Kuru, there's been no detectible infectivity in those specimens either.

DR. HOLLINGER: Is that like, Paul, there's been no evidence of transmission through blood transfusions either?

DR. BROWN: In primates that is true.

DR. HOLLINGER: And were the experiments in milk, were they cross-species experiments or were they in the same species?

DR. BROWN: Well, we never inoculate humans, but in chimps and moneys, they were negative from humans. So that's about as good as you can get in terms of closeness of species.

Is either Dr. Healey or Kay Gregory in the room now?

MS. GREGORY: Hi. I'm Kay Gregory.

DR. BROWN: Hold on just a second, Ms. Gregory.

MS. GREGORY: What I wanted was to ask if I may speak after the afternoon session because I think my comments are more appropriate after you've heard the presentation from the NBDRC.

DR. BROWN: Okay. Dr. Healey. Is there

any other person in the audience who wishes to make a public statement?

In that case, are we ready from Ireland? Fine. Here's Dr. Molloy from the Clinical CJD Surveillance Unit, St. Vincent's Hospital, Dublin, Ireland, and she will talk about the surveillance of variant CJD and the potential human exposure to BSE in the Republic of Ireland.

DR. MOLLOY: I'm probably going to overlap on some of the details and maybe clarify some of the issues that were raised in the questions section before lunch. Could I have the next slide please.

I'm going to talk first about BSE in Ireland. The first case was identified in 1989 and BSE was made a notifiable disease at that stage, and the action taken at that stage was that all imported meat bone meal from UK was banned. In 1990, all ruminants derived meat bone meal was banned for both sale and use, and there were controls on UK imports. That means that they were prohibited, and then in 1996, more legislation was brought in. All previously imported UK livestock was slaughtered. All birth cohorts, that means cattle under six months who were residing on the same farm of cattle

that had been diagnosed with BSE were slaughtered and progeny of BSE positive animals were slaughtered. And this was all done in one plant. There was also a ban on ruminant rations in meat bone meal derived from poultry or pigs, and in total, in the last 11 years, we've had 474 cases of BSE. These are mostly indigenous. However, there have been 15 imports. The majority of these have been from the UK or from Northern Ireland. However, it's interesting to note that one was from Denmark who didn't have a case of BSE until this year, and one was from the Netherlands. Next slide please.

So what we do if we find that there is a cow with BSE, the herd is quarantined on the basis of clinical suspicion. If BSE cannot be ruled out, the suspect is slaughtered. The brain is then examined and if BSE is confirmed, the entire herd is slaughtered in a special non-export meat factory. The progeny are traced and slaughtered and the birth cohorts are traced and slaughtered. Next slide please.

This came up for debate. What exactly is specified risk material? This is the material that's excluded from human and animal food chains and concerns the spleen of sheep and goats, the

skull, brain, eyes, tonsils, spinal cord of cattle, sheep and goats over 12 months old. And these are audited at all the rendering plants in Ireland by the Department of Agriculture daily. Next slide please.

In the UK and Portugal, they have slightly different legislation regarding SRMs, and this is just from our Department of Agriculture, what we have been told and in the UK and Portugal, SRM includes the entire head excluding the tongue, thymus, spleen, intestines from the duodenum to the rectum, so not including the stomach and cord if the cow is over six months, and also the vertebral column including the dorsal root ganglia of animals over 30 months in the UK and this has recently been changed and over six months in Portugal. Next slide please.

So in order to control BSE in Ireland, the main action taken is that there's an antemortem examination of all cattle for clinical signs of BSE. There's the removal of SRM material from the food chain. There's an inactivation of any possible BSE agents in the SRM free offal, and there's hopefully prevention of cross contamination of ruminant feedstuffs with SRM. The aims of these are

obviously to remove the possibility of cattle exposure to BSE agents through the contamination of feed and to insure the safety of Irish beef.

So what are our figures. In 1995 and up to 1995, the numbers of BSE cases were very small and they were in the teens, below 20. However, in 1996, this rose to 73 and this is unexplained. It's not sure whether there was a real increase in instances of BSE or there was a change in the level of recording due to publicity of the disease. Since then numbers have been in the seventies rising to 95 in 1999, and in January to March of 1999, last year was 27 cases and this again has risen this year, and it's not sure again, it's thought that this is due to inadvertent exposure to feedstuffs contaminated with BSE agents in the early and mid-1990s. Seeing as the main, more stringent controls were instituted in 1996, it's expected that the instance of BSE will decrease in 2001 at the earliest. So even though our numbers are rising at present, we are expecting that. Next slide please.

There's some interesting comparisons to be made between, what can be talked and can't be talked about, without mentioning the north versus the south. The border counties, these are the

counties bordering Northern Ireland but actually in the Republic of Ireland, have had a higher incidence of BSE. For example, you can see from the figures demonstrated there that the number of bases of BSE on the border counties have been 69 with an incidence of .84 when taking into account the entire population whereas for the rest of Ireland, there have been 196 cases but when taken into account with the cattle population, the incidence is .31. The border counties are listed there. I have a little map of Ireland just in case anyone isn't sure where we're talking about.

So in total from 1989 to 1997, there were 265 cases of BSE infected cattle. These were all cows but one imported bull and they were mostly dairy stock. They were mostly born between ages of 1981 to 1994 and the average age was three to 10, and the average was five. Northern Ireland in comparison have had 1,766 cases of BSE in the same period and Great Britain has had 170,885. So even though our numbers are still rising, they're still relatively small.

The difference between the Republic and the north of Ireland has been based on different farming practices and this includes using grass for

milking and calf production. There's a lower dependency on ruminant-derived protein feeds in calf rearing in the Republic and most of the imported ruminant ration from the north was mainly used in the border counties, explaining the increased incidence of BSE in that area.

So from BSE to CJD, in 1996, we started looking at CJD seriously in Ireland. This is in line with the European collaboration which Bob has already mentioned to you. We have some retrospective data on CJD in Ireland dating back to 1980. So we feel that we have accurate data for the last 20 years of CJD in Ireland. The retrospective study took place until 1996 and this concerns death certificates and neuropathological data. There are only two neuropathology centers in Ireland, one in Cork and one in Dublin. There were 20 cases identified and there is data available on 15. This gave us an annual mortality of up to 1996 of .31 per million. Next slide please.

Here's my little map of Ireland. Okay. These are the border counties here where there is an increased incidence of BSE. However, you can notice that the data on Ireland for CJD. The only predominant area involved is Dublin which is here

with 13 cases and that's because it's the most concentration of neurologists really. The population of Ireland is 3.8 million and about 1.5 million would live in this area here. In contrast, probably about 1 million live down here but there's been a marked decrease or low number of CJD in that area and the west traditionally is not associated with cattle farming. So that would explain if there was any if there was any link between BSE and CJD, the low numbers there. Next slide please.

In 1996, CJD was made a notifiable disease in Ireland and after surveillance was commenced. This was on the basis of a CJD advisory committee which was set up between the Departments of Health and Department of Food and Agriculture. These have monthly meetings. Postmortems are now done in the two centers. It's now been really confined to the Dublin area for CJD surveillance. Next slide.

Since 1996, we've had 12 cases of definite CJD all with neuropathological confirmation and data available on 11. There's been one genetic mutation at codon 178 but the rest apart from one have been sporadic. The features of these are atypical of those described as sporadic CJD.

The risk factor is two as of the 11. As we know, we have spent a significant amount of time in the UK. One worked in a meat processor and one worked as a leather factory worker.

After surveillance began last year in July with the formation of the unit base between the clinical center and the neuropathological center, this is modeled under surveillance unit in Edinburgh and we notified all physicians, neurosurgeons and psychiatrists of the risk factors for CJD. Because there are so few neurologists in Ireland, we felt it important to extend notification of this to all general physicians and psychiatrists.

Since last year, we've had 10 referrals, four to the clinical side and six to the neuropathology side. Seven have died. We have two cases of sporadic CJD and there you have a list of the three cases of alternative diagnosis and we had one case of variant who presented clinically last May, in May of 1999.

Just a few details about that. It really fits in the bill with the rest of the cases of variant CJD, the one represented from France. She was a 33-year-old mother of two. Presented with pain in the right leg, unsteadiness and depression.

Collateral from her husband confirmed the depression and also some psychiatric symptoms. Her past history was unremarkable. The family history was unavailable because she was adopted and she worked as a chef. She was from the Midlands of Ireland plus had significantly been a resident in the UK for six years between 1989 and 1995. She was also a blood donor when she was in the UK and obviously the UK Transfusion Board was notified of this at the time and all the blood products where withdrawn. On examination, she just had features which confirmed the clinical diagnosis of CJD. Next.

Investigations were typical as well, were suggestive to with the 14-3-3 protein being positive. The EEG was abnormal. The MRI showed the high signal's abnormalities described in variant CJD. If you show the next slide, it just shows them there, in the pulvinar region of the thalamus. Next slide.

So this data here refers to the CJD surveillance in Ireland over the last 20 years. In 1998, we had six cases but we think this is because of a backlog from and suspicion from the other years, but generally overall it's been petering out between one to three per annum of cases which would

fit in. Next slide.

This is of our BSE, again 1989 the first case diagnosed and then in 1999, 95 cases and again rising figures for this year.

So if we combine the data for the CJD in Ireland, we had 32 cases for 20 years. The annual morality worked out at .44 million and we were a bit concerned about this as to whether it was under ascertainment. But on talking to several of the UK surveillance units, they mentioned that there were similar numbers described for Northern Ireland for CJD and there's a regional variation described in the UK. Next slide.

Obviously there are problems with the surveillance of CJD which are universal. It's a rare disease and there are uncertainties and have been uncertainties in case definition. They are developing diagnostic techniques and there's a geographical variation and risk factors for CJD particularly with the UK.

But in Ireland we have our own problems, next slide, particularly because of public awareness and we have a very agricultural based economy. So it tends to be a little bit of brushing it under the carpet. Obviously the data is all there but it's

not liked to be publicized that the Irish beef could be contaminated. And the data that we have is real, and also the diagnosis made by postmortem. There's been a controversy about doing postmortems and retaining organs in Ireland recently. So that will make it more difficult in the future to gain consent for postmortems to confirm the diagnosis of CJD.

I have a slide at the end. I don't know if we can show it, it's just a cartoon. Anyway, this basically shows our Tolnista. That's the equivalent of our Deputy Prime Minister or Vice President, and this over here says "Beef heart", a referral to a particular film that was out most recently and basically what he's saying if you want to interpret in the right way, not British beef anyway is what it says. There we go. It refers to mind the border against Sasanach. That's the English. It's a joke. I hope Bob won't take offense.

And the other thing was, one of the details that arose earlier was questions on the annual incidence of BSE in Ireland and I did get some information from one of the documents that I have, which you can show. I don't know if this will help clarify some issues. The annual national

incidence confirmed clinical cases of BSE between '95 and '97 expresses a percentage of the cattle population for these various countries. This is the data that we were given from our Department of Agriculture. So for example, in Ireland in 1995, 16 cases, incidence .22 per 100,000 of cattle compared to Great Britain, 14,300 cases, incidence of 119.16 per 100,000 cattle. I can get that photocopied if anyone wants that. Okay. Thank you.

DR. BROWN: Thank you, Dr. Molloy. Before we hear from Dr. Giulivi, I have a question I think maybe for Bob Will. I'm not sure. Yes, again. For what are a heart and lung used from cattle? They're not specified risk materials. What happens to them? Do you know?

DR. WILL: I honestly don't know the answer to that question. It may well be people from the agricultural world would know far better than me.

DR. BROWN: Linda.

DR. DETWILER: I can't speak for Europe but I know in the United States, heart can be edible for human consumption and lungs in the United States are not for human consumption but they most of the time go into pet food or animal feed.

DR. BROWN: The reason I ask this is simply because of the demonstration by a number of studies that depending on the method of stunning cattle, brain emboli wind up in both the heart and lungs and as they are not to my surprise today included among specified risk materials, I was curious to know where they do wind up. Bob.

DR. ROHWER: If you're going to raise that issue to the extent that brain emboli end up in the heart, they end up in the whole circulatory system because they get there via the aorta.

DR. BROWN: Well, actually that's not so, Bob. Experimentally it's not so, and theoretically it wouldn't be so either because they would be going through the venous system from the brain. They can, however, reach the liver and they've been demonstrated to reach the liver through the connection from the portal vein system and the peri-spinal venous system. So under pressure, when you mash up the brain as is sometimes done, emboli under pressure can reach the liver directly and presumably from the liver elsewhere.

DR. ROHWER: I'm not talking about the emboli per se, but just the idea of having mashed brain tissue in the circulatory system in a still

beating heart, probably delivers the thing throughout the whole body.

DR. BROWN: Yeah, but the circulation is such that in the venous system it comes down the vena cava into the right part of the heart, goes through the lung and is trapped in the lung. That's been the experimental demonstration. So it's conceivable that emboli, very small emboli might escape. The only study to date that's been concluded, two studies actually have looked at muscle in cattle in which emboli have occurred in the lungs and the muscle does not have emboli and in fact, of the studies that have been done, no emboli have ever been described in the peripheral arterial system, the peripheral blood system which isn't to say it might not happen, but the studies to date have failed to demonstrate it.

DR. ROHWER: I guess what I consider a more stringent test of this idea would be the actual titer of infectivity in the blood collected from an animal that had been stunned, and I would guess that it would be greater than the titer of infectivity that would be in the blood of an animal that hadn't been stunned.

DR. BROWN: Bob.

DR. WILL: Could I ask you a question? My understanding was that the type of stun gun that was used had an effect on the chances of embolization. I wonder if you'd like to comment on that.

DR. BROWN: Yeah. The embolization has occurred almost exclusively in cattle that have been stunned with an air-injected so-called captive bolt. It's a system by which something that looks like a pistol fires a bolt which penetrates the skull of the cow and stuns it and then one variety of such a bolt, then inoculates or injects compressed air through the bolt that is penetrated which basically makes scrambled eggs of the brain and that has been associated with emboli fairly consistently. The second procedure that's been associated with emboli no matter what kind of captive, well, as long as it's a penetrating bolt gun, sometimes one method is not to use injected air, but then to run what is called a pithing rod which basically does the same thing into the brain and agitate it. So these are the two stunning methods which have been associated with emboli and I understand from Ray Bradley that the air gun is not used in Great Britain but pithing has been a practice and air guns are used elsewhere

in the world including the United States and some countries of Europe. Sorry for that diversion, but I have to get things out while I still remember them.

Dr. Giulivi, we're going to have a model quantitative assessment of the risk. Actually, Tony, I'm not sure if that shouldn't be a quantitative model assessment rather than a model quantitative assessment. You're prejudging your presentation before it's made, of the risk of variant CJD in Canadian travelers to the UK and France, and this is a very interesting model system as I'm sure you'll agree after you've heard about it.

DR. GIULIVI: I'd like to thank the Committee for inviting me and I'll have the first slide.

What's happening in Canada is what's happening in the United States. We're assessing the risk of variant CJD now for France and we'll get into the story more why we're doing that for both the Canadian travelers to France and the UK and then for the blood supply.

Now we have not come to a conclusion or anything. We're still in the process of evaluating

a lot of data and bringing that date forward. Next slide.

One note is that the risk assessment that you'll be seeing here is a little bit different from what we presented in March and Dr. Brown was the Chairman of that Committee. Under that Committee's recommendation, they proposed that maybe we should do two models and see if the predictions of the number of travelers coming down with the disease, the probability of coming down with the disease, and the prediction of how many people in France are coming down with the disease, compare to each other and then use that model for the blood supply, and that's what we have done, and you'll see that. Next slide.

Just an introduction and I don't want to go through all of this, but Health Canada Policy which is done by our regulators, we function as a risk assessment surveillance group, LCDC. The regulator people will function as a regulation policy. When they have to do a risk assessment, sometimes they come to us because we have the surveillance part of that activity, and we will assess as a third party independently and being a forward to a committee which is called the BTOX

Committee which is addressed by our regulator, present that data to them. Then they bring it forward for policy development, if they agree or not agree with the data.

Now they're the ones that asked us because of the situation in France to reassess our risk assessment that we done before this which was the UK and reassess for France and now we're reassessing for most of the countries in Europe. Because of what you have heard this morning, we're going through the same exercise in getting data and assessing using our models. Next slide.

So when we say a comprehensive review of risk, we have divided our risk assessments into internal and external and internal is the domestic cases and food imports into Canada first. So we're looking at what we have imported from outside to inside, what's the risk of that compared to what they are to risk because we have to know if we did import or not import, and that took time to get all the information. We had one cow imported that came down with CJD out of the 200 and all of them were slaughtered and it was originally from the UK. I think it was 400. Yeah, one in 400. And we had some lawfuls coming in, but the amount of losses

you'll see in the following slides are very, very little.

Then we looked at the travel of BSE countries. Our Canadians travel to Canada and to UK, assessing the risk of traveling to the UK, assessing the risk for that. Then for the question on do we add the deferral or not as a risk assessment, so we're looking at detailed forecasting of using BSE and CJD cases and basing on that forecast, we're predicting certain numbers and that will move forward. We're also looking at the impact of blood supply and that is going to be done like it has been done in the past by the blood system, Hema-Quebec and CBS and they have information there, and then we're looking at other countries. Next slide.

For the impact of the blood supply, Hema-Quebec and CBS and you'll hear from them later on, their data, what we did is we received their data and we just combined the data to represent as one, and we took the higher numbers and I'll explain that when we get there, the higher numbers. Like there's two sets of data and CBS has a certain set, Hema-Quebec has a certain set and you have a range. To be prudent, we just took the higher range.

The travel length assignment and the

risk percentage was done by Hema-Quebec and CBS, but the travel by length of stay was an assumption that we had to get from Stats Canada, and then CBS, the blood supply, CBS is doing a residual risk of recruiting donors and we're looking at the impact of residual risk of recruiting new donors and how that's a true risk. If you're losing donors, you have to recruit these donors and what's the true risk of certain other viruses and that's going to be in a collaboration with the blood system and also with other hospitals. And this is a study that I have with about six hospitals. The probability of death from shortage of blood supply in the ICU and trauma. Next slide.

The Blood Borne Pathogens Division and you'll see there the two now going to the tables has undertaken this type of analysis or scenario analysis and Monte Carlo Simulation, and I'll go into that more later on. The factors that we included is our model takes into consideration the number of variant CJD in France and in UK, the estimated number of slaughtered BSE infected cattle and the infectiousness of the bovine tissue. These are all hypothesis but especially this one. This is data got from surveillance. And then we used other

available information to use various scenarios to estimate the theoretical risks and this is my waiver for Canada is that "this work demonstrates the extent of current uncertainty" right now, and caution must be used to interpret the results which, you know, we are doing that, but at least we're getting some numbers. Next slide.

So the first method that you heard about was presented to our TSE Advisory group and it was divided into two parts. One part is this part here which is using Monte Carlo and a technique called Markhov Chains Analysis and it's based one important fact, based on the numbers of CJD in France and in UK. So that's 61 or 60 whatever it was at that time, was 61 people in the UK and we took into consideration at that time the third case in France. And we had to use it as a proxy and exposure rate. Now these numbers are low and in theory we could do that because the numbers are low, and then did an analysis of that. We also then used the estimation of risk in France as we did with the UK based on the cattle exposure or the portion of food lawfuls that went into France and that was easy because we got it from the French surveillance group confirmed. We were doing it separate but, you know, we got the

same figures of 10 percent and so on. So we were happy that we got the same results and we just reported here. This analysis method too is different from theirs and this is using a study that was conducted by Wellcome Trust using these numbers of estimated BSE cattle and using the number of infectivity agent from that study, and that's a study based analysis with using a Monte Carlo Analysis after that. We did that to compare if we were going to get the same numbers of prediction of people coming down with the disease in France, the probability of the people coming down, our Canadian travel, and they were comparable. What we predicted here at the end of this year on using this model and we take and considered the genetic, you know, math and so on, and these are all hypothesis in that we assume that there should be five cases by the end of the year and plus or minus two. What we predicted from this is about six plus or minus three. So they're corresponding to each other and that number three, they're probably increasing in France, it seems that it is true. So our model does reflect that. We're predicting nine cases in France by the year 2003 I think it is, another extra nine cases, and in that predict about 10. And then it slopes

down and what we're predicting for the UK is that this 10 or 12 cases per year which is obvious because we're using those numbers, so predict what is happening. Next slide.

So as I stated before, this is the available information we've received and what was similar for France, what was unlike with the consumption. Next slide.

And at that time we were working with figures of 52 with 9 probable cases and that's 700,000 Canadian visits per year to the UK mostly from big cities and approximately, this is the 100 percent of beef, that's not the 100 percent of all beef, that's, you know, the beef was contaminated. That's what I mean by 100 percent and that the number of diagnosed cattle we used. Next slide.

We used these figures from France, two and this probably case. This figure of 350,000 Canadians visiting to France we got from Stats Canada. Stats Canada has a surveillance program for travelers and I think it's used for income tax purposes, that when you step into Canada, they give you I think it's one in 100 person that steps in the border, they give you this survey to fill out and that's how we got that information going back 10

years and that's approximately per year. This comes from various resources that confirm each other from the French Embassy, from France surveillance group, from our own internal food people and this also from our internal food people. Next slide.

This is where in the model we make major hypothesis. The incubation period is unknown. So we ignored that. We said forget about it. We don't even consider it. We do the model without that.

The minimal dose and, you know, the cumulative dose, we don't know that. So we just say this is roulette type game and we made a hypothesis that it is based on a chance.

The distribution, we did not know so we had to make assumptions there and this is another thing that we don't know about. So we had to make the assumptions that they're equal. Next slide.

The infective agent is assumed to infect all ages and genders alike, a certain age group, and that it is similar from BSE, both from France and from Britain. These are all assumptions that went through out TSE Advisory Committee in March and there was a lot of discussions on that and this is the consensus of what was happening. Next slide.

The travel pattern and dietary remains

constant over time. That's another assumption. The other assumption that we made that you have one meal containing a specific risk during that time period. We made that assumption, and this is the export/import related between the countries and, you know, British exposure, contamination is 10 times higher than the French. Next slide.

Then we looked at our imports to Canada and to see if we have an internal risk, a theoretical and internal risk. This is how much we imported in kilos, not in pounds, but kilos, during this time period and that's total meats. That's offals, processed meats, cattle and so on. These are the imports from each country. We could not get anything from Portugal. It was very hard to get anything at all and we still have nothing. We're about 90 percent self-sufficient. The rest, 10 percent, comes from elsewhere and most of that comes from the United States. And then you can see from the United Kingdom that 0.02 and .007. This includes all meats. So when you just look at the lawfuls or the high risk meats during that time, it was like 0.002. It was very low. It was only about 100,000 kilograms, something like that over that period of time. Next slide.

So then what we did is using the model and using both models and averaging out, the prediction of a person traveling with length of time and the prediction of that person coming down, being exposed and exposure for us means disease, okay, and even though it's not true, we took that. And you can see the difference between UK and France and the ratio here is 16 times difference, is 30 times difference and here's 20 times difference. Why we did this is because we're looking at, if we extend the policy or do an assessment and bring this forward to the regulator, what we felt important is the additive effect of introducing a policy, you know, is it 16 times more or 16 times less versus the true risk of introducing a low blood supply versus infections. So these numbers are important because that's the relationship. Next slide.

So if you look at it in percentiles and you look at UK, one month stay for us is 5 in 10 million, the probability of acquiring the disease, six months three and so on. We have predicted because we have quite a few travelers from the age of 14 to 40 in certain big cities like Toronto, that with our surveillance program, we have predicted that we should see one person in Canada with variant

CJD because of the travel through the UK within the year, within the 10 to 12 months, and that has, you know, that information has moved up the line. It's a lot about travel and the cumulative risks of staying there, something like the risk that you just heard from Ireland. Next slide.

When you compare that to France, you can see it's much, much lower, okay. In theory, it's much, much lower. Next slide.

This data, what we did like I said comes from CBS and Hema-Quebec. We just combined the data and took the highest number to be prudent and CBS and Hema-Quebec will review this, I don't want to get into details, just what we're looking at here is reduction. If we do put a policy or recommend something, what is the reduction of risk and then factor in that thing, that number, probability that I said one in 16 and so on, into that, and then factor in the true risk of blood supply and infectious disease. So that's the procedure we're moving forward in LCDC, to move forward this type plan. Next slide.

This is for France. Next slide.

And so in summary, like I said, we haven't drawn the conclusion. We're just doing this

risk assessment to move forward to the regulators. Any decision in my of view has to account the relative risk and true risks versus the blood supply giving those numbers in our models. Thank you.

DR. BROWN: Thank you, Dr. Giulivi. We have now a shed of three papers which will conclude our education this afternoon. The first is a reanalysis of U.S. blood donors particularly with respect to European travel outside the UK. The second will be the implementation and effect of such deferral policies on the U.S. blood supply, and the third is the effect of implementation with respect to UK deferral data. The first presentation is by Dr. Watanabe from the WESTAT, INC. in Rockville.

DR. WATANABE: I'm representing the American Red Cross ARCNET and the NHLBI REDS project and in cooperation with AABB and ABC.

As you've seen in Alan's talk last year, he listed all the blood centers that participated.

The travel survey objectives included these two main points. The first one, that the survey was designed to estimate U.S. donor travel in United Kingdom and Republic of Ireland for defined periods in 1980 to 1989 and 1990 to 1996, and to also look at associations between travel in the UK

and donation variables such as first time, gender, education.

The survey design, it was not designed to measure non-UK BSE exposure. There was disagreement as to whether this information should be collected.

The travel survey methods, it was a random survey, random sample of donations in December of '98 and January of 1999. We sent out 19,000 anonymous OPSCAN forms and it included a single mailing with a cover letter. We didn't send a second mailing out or anything subsequent to that. The data I'm presenting today is an update to what Alan presented last year. It's current up to July 20 of 1999. Approximately 50 percent of the people who received the questionnaires responded.

The travel survey as you seen last year included demographic characteristics, donation history and travel and residence in the UK which included Ireland and it also included a kind of broad question about travel in non-UK BSE countries. It also included beef ingestion while in the UK and overall in the past year and it also included deferrable risk estimates.

On the questionnaire the question about

non-UK BSE was stated, did you travel to or live elsewhere in Europe? And it listed all these countries, and the donor had the option of marking one or all of the countries. And if they did answer yes to these countries, then it broke down the two time periods again.

From Alan's talk last year, these are the numbers or pretty close to the numbers that he presented last year where for the entire period 22.8 percent of the donors had traveled or resided in the UK. From our analysis now, we've looked at also overall the non-UK BSE travel prevalence and it's 23.7 percent. The combined travel prevalence for these donors is 32.1 percent. Of this 32.1 percent, 14.4 percent of the donors traveled to both the UK and non-UK BSE countries.

Now addressing the question of France, for the entire period there are 27.5 percent that indicated that they had traveled or resided in France and the UK. Looking at France alone without the UK was 4.7 percent.

Now just looking at the crude prevalence by country, non-UK BSE countries, it ranged from 15.6 percent to 2.2 percent for Portugal.

Because the questionnaire was not

designed for non-UK BSE countries, it was difficult to tease out any specific country especially if a donor answered more than one country on that open-ended question. In the questionnaire, there were approximately 1,500 who indicated that they traveled or lived in France. Of those, 70 percent also traveled or lived in the UK, and of the 1,039 who traveled or lived in the UK and France, 72 percent of them also traveled or lived in one or more of the other BSE countries. Of the 447 who traveled or lived in France but not in the UK, 58 percent of them also traveled or lived in one of the other BSE countries.

Now this graph is the same thing that Alan presented last year, and it shows that two percent that responded that they had traveled or lived in the UK five to eight months. Alan had also presented a table showing these numbers are adjusted prevalence for first time and repeat donor response to the questionnaire, and he came up with lost units and this 2.2 percent is what is often quoted in the literature and from Alan's talk.

Now I looked at all non-UK BSE countries and the prevalence using the same duration of travel or residence, and for non-UK BSE countries at about

one month, there's 21.2 percent; at six months, 4.8 percent; and at about a year, it's 2.9 percent.

Now when I looked at donors who indicated they went to the UK and/or non-UK BSE countries, the prevalence then becomes 27.7 percent for about a month; 7.2 percent for six months; and 3.9 percent for one year.

When travelers went to Europe, they didn't just go to one specific area. They often went to many different countries especially looking at the France data, 70 percent or more went to other countries non-UK BSE countries. I tried to come up with an estimate based on 10 percent. What I did is taking the UK data, I took 10 percent of the total non-UK BSE cases in each interval and added them to the UK cases at each interval to come up with, this is just a very rough estimate of taking 10 percent for France. At one month it was 13.4 percent. At six months, it was 2.6 percent and at one year, 1.5 percent.

This graph is just basically showing what two or three of the previous tables had, the data that it had. Looking at about a month, this is a difference. The first bar is UK only, the second bar is UK and France, and the third bar is UK and

non-UK BSE combined. This here is one month, this is six months, five to eight months, and one to two years is here.

Now from Alan's talk last year, he also came up with not only the 2.2 percent of blood supply loss if you took a duration of six months, but also 86 percent of the person days at risk would be captured at six months. I also applied that to the total non-UK BSE cumulative person days at risk and it's 88.4 percent.

I'd like to thank my collaborators and the PIs at the other blood centers. Thank you.

DR. BROWN: Thank you very much, Mr. Watanabe. Dr. McCurdy from the National Heart, Lung and Blood Institute, the National Institute of Health, will now tell us about the implementation and effect of recent changes in deferral policy on the U.S. blood supply. Dr. McCurdy.

DR. McCURDY: Thank you, Paul. Starting a bit more than a year ago, as a result of some decisions that were being made and expected to be made regarding the deferral of blood donors, a strong recommendation was made that some means of surveying the blood supply to detect shortages, it was hoped that there might be trends that would

detect shortages before they occurred, but at least to have some data. The Heart, Lung and Blood Institute arranged with the National Blood Data Resources Center to collect data from a sample of blood centers around the country and will shortly begin to collect data from a sample of hospital transfusion services to fulfill that interest in seeing what the blood supply was.

Data began to be collected in October, was made available to us at the NHLBI sometime in January and we've been collecting monthly data since that time. Monthly data was specified rather than annual or semiannual because we felt that it was necessary to look at seasonality and other aspects of the available blood supply. Can I have the next slide please?

There were several sampling strategies that were looked at. The one that was selected had a larger proportion of cities because our major purpose was to detect shortages. It is likely, however, the way the samples were collected that they are representative of the country. There were some blood centers who were not able to participate and the final sample was 26. Ms. Sullivan will discuss some of this in greater detail when I