TRANSMISSIBLE SPONGIFORM

ENCEPHALOPATHIES

ADVISORY COMMITTEE

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P R O C E E D I N G S (8:02 a.m.)

DR. FREAS: Mr. Chairman, members of the committee and the general public, I would like to welcome you to the second day of the TSE Advisory Committee meeting. I'm Bill Freas, the Executive Secretary for the session. Today's session will be open to the public, the entire session will be open to everybody, and you are more than welcome to stay for the entire session.

Now I am going to go around the room and introduce to the public the members of the committee, and would the members again please raise their hand as there name is called. And starting on the right side of the room, that's the audience's right, the first chair is occupied by a temporary voting member for today, that's Dr. Raymond Roos, Chairman, Department of Neurology, University of Chicago. The next chair will soon be occupied by a member on his way, that will be Dr. Bruce Ewenstein, Director, Boston Hemophilia Center, Brigham and Women's Hospital. Next we have with use a standing committee member, Dr. Pedro Piccardo, Associate Professor, Indiana University School of Medicine.

Next is a temporary voting member for today, Dr. Russell Crawford, Executive Director, Association of American Veterinary Medical Colleges, Washington, D.C. Next is a standing committee member, Dr. Ermias Belay, Medical

Epidemiologist, Centers for Disease Control and Prevention. Next is a standing committee member, Dr. Elizabeth Williams, Professor, Department of Veterinary Service, University of Wyoming. In front of the podium is a temporary voting member, Dr. George Nemo, Chief, Blood Resources Section, Division of Blood Diseases and Resources, National Heart, Lung, and Blood Institute.

Around the corner of the table is Dr. Pierluigi Gambetti, Professor and Director, Division of Neurophathology, Case Western Reserve University. Next is a temporary voting member for today, Dr. William Blackwelder, Biostatistical Consultant, Biologics Consulting Group, Alexandria, Virginia. Next is a temporary voting member and also a representative from FDA's Blood Products Advisory Committee, Dr. David Stoncek, Chief, Laboratory Service Section, Department of Transfusion Medicine, NIH.

Next is the Chairman of this committee, Dr. David Bolton, Head of the Laboratory of Molecular Structure and Function, New York State Institute for Basic Research. Next is Dr. Peter Lurie, Medical Researcher for Public Citizen's Health Research Group, Washington, D.C. Going around the corner of the table, next we have Dr. Stephen DeArmond, Professor, Department of Pathology, University of California San Francisco. Next is our consumer representative, Ms. Shirley Walker, Vice President of the Health & Human

Services, Dallas Urban League.

Next is a standing committee member, Dr. Suzette Priola, Investigator, Laboratory of Persistent and Viral Diseases, Rocky Mountain Laboratories. In the empty chair we will soon be joined by Dr. Paul Brown, Medical Director, Laboratory of Central Nervous Systems Studies, National Institute of Neurological Disorders and Strokes. Next is Dr. Dean Cliver, Professor, School of Veterinary Medicine, University of California, Davis. Next is a standing committee member, Dr. Lisa Ferguson, Senior Staff Veterinarian, U.S. Department of Agriculture. And next is our industry representative, Dr. Stephen Petteway, Director of Pathogen Safety and Research, Bayer Corporation.

I would like to welcome everybody to the meeting this morning, and I would just like to make a statement that the conflict of interest statement for this meeting was read into the public record yesterday and that still applies to today. Mr. Chairman, I turn the microphone over to you.

DR. BOLTON: Thank you Bill. Before we begin this morning I just want to make a couple of comments about a reference that was discussed or brought up by one of the members of the public yesterday, and that is a paper that has just recently appeared on the science online web site, Science Express, and it deals with the, well the title of the paper is The Predictability of the U.K. Variant

Creutzfeldt-Jakob Disease Epidemic. And the way that the paper was brought up yesterday seemed to indicate that this paper was showing that the vCJD epidemic was almost certainly at its peak and soon to be on the decline.

I downloaded the paper last night and read it, and there are a couple of comments I would like to provide to the committee and to the public at this time. The paper is essentially a statistical analysis using, it's a back calculation analysis of the epidemic. And while it uses statistics that are far beyond my expertise, it also makes many assumptions about the disease that I think are questionable, in particular, assumptions about the incubation period. And while I am confident that the authors are far better statisticians than I am, I am not sure that they understand the diseases quite as well those on this committee.

Critical features are that the model does not appear to incorporate known features of prion disease incubations, and that is first of all that the incubation period is inversely proportional to the dose, so at lower doses incubation times are quite long. The incubation periods also vary at doses, very substantially at doses at or near the end point, so that at the very lowest doses, the incubation times can vary most widely. And the fact that whether an individual becomes infected or not depends

somewhat on statistical probability, and that is clearly reflected in experimental animal studies, where at the very lowest doses, the incubation periods vary widely and may or may not actually infect animals or other individuals probably that were actually inoculated.

So I think that while I am sure I can speak for myself, I certainly hope that they are right in predicting an epidemic that perhaps includes only several hundred affected individuals. I'm skeptical that that is in fact correct. And in fact in their own abstract they state the model indicates that current case data are compatible with numbers of infections ranging from a few hundred to several millions. In the latter case the model suggests that the mean incubation period must be well beyond the human life span, resulting in disease epidemics of at most several thousand cases.

Now that statement seems to be somewhat incompatible with the previous one of several millions. But in any case I think that we should be careful in interpreting statistical papers like this, models of an epidemic that has, as far as I can tell, not yet reached its peak.

Also with respect to this, I would like to briefly bring up another paper that was also just recently published. This I downloaded from the Journal of Aerology

site and it is by Richard Race and colleagues at the Rocky Mountain Lab, colleagues of Dr. Priola, and this is relevant both to the statistical paper and to other discussions, and the paper is entitled Long-Term Subclinical Carrier State Precedes Scrapie Replication and Adaptation in a Resistant Species, Analogies to Bovine Spongiform Encephalopathy in Variants Creutzfeldt-Jakob Disease in Humans.

That title unfortunately is a bit long, but basically what the paper describes are experiments in mice, where the mice were infected with the hamster strain 263K of the prion agent, and previously studies have shown apparently that mice were not infected by this agent. But unfortunately those studies had only been carried out to a time period of about 300 or so days. In this paper they show that mice that are infected with this hamster agent do not produce mouse PRP scrapie nor do they produce mouse prion infectivity for more than a year. During that time hamster prion infectivity is detectable in the early stages and then probably is irregularly detectable over that time.

After a period of about a year, and for the most part in periods of 600, 700 days, the mice then begin to show mouse prion infectivity and later mouse PRP scrapie, but that really only occurs after passage to a second animal. So I should correct myself. In the first passage the mice are asymptomatic throughout their entire life span,

and they do not show PRP scrapie. If those homogenates from the brains of those animals are blind passage in subsequent mice, the second mice then begin to show PRP scrapie and infectivity, and an interesting aspect is that the biological characteristics of the agent begin to change and new strains appear, some of which appear to infect both hamsters and mice, others of which apparently infect mice preferentially.

So this is a caution in the sense that we don't know what in crossing species varies exactly, what the incubation period is going to be, nor do we know what the biological characteristics of the agents will be. And as I read this paper last night, I begin to think that we must be cautious about other species, for example pigs, that are now thought to be not infected by the BSE agent or not readily infected. And perhaps they may exhibit extremely long incubation times, perhaps even exceeding the normal life span, before they show clinical disease, but in fact might be harboring and developing prion infectivity that would infect others of that species, as well as have a broader host range.

So as the member of the public stated yesterday, we should make decisions based on science. This is real science, and what this science tells us is we do not fully understand this disease and how it is transmitted and the

characteristics, the biological characteristics of the agents. So I do think that we should be very careful when we make our deliberations to remember the degree of uncertainty that is involved in these agents and diseases.

So having said that, I'll step off of my soap box and move to the first topic, which is Topic 3, Bovine Brain, Spinal Cord, and Other Neurological Tissue in Foods, Drugs, and Cosmetics for Human Use, and Dr. Robert Brackett, from CFSAN, FDA, will provide an overview and background. And I think Dr. Brackett will tell us what CFSAN stands for.

Agenda Item: Overview and Background

DR. BRACKETT: Thank you Dr. Bolton. Good morning. My name is, for those of you who don't know me, my name is Bob Brackett, and I am Director of Food Safety and also serve as the Technical Aide for the Center for Food Safety and Applied Nutrition, CFSAN, which is FDA's branch that is responsible for regulating cosmetics, dietary supplements, and most foods other than meats and poultry products, and these products are regulated by the Department of Agriculture.

This morning we are bringing before the committee the subject of bovine brain and other neurological tissues from bovine that would be in foods, certain drugs, and cosmetics that are intended for human use. And the purpose of our bringing this is actually because bovine brains and

other neurological tissues could constitute a potential food, drug, and cosmetic safety hazard. FDA seeks the input of the TSE Advisory Committee in determining the benefit, if any, of restricting the use of bovine neurological tissues and products containing or contaminated with these products or manufactured from the tissues in foods, drugs, or cosmetics for human use from these products.

And the reason behind this request is as follows. It is well accepted within the scientific community that neurological tissues are the most highly infective tissues in BSE infected cattle, and in fact that the majority of the infectivity of these cattle resides within these tissues. Currently these tissues may be used directly as human foods, these are primarily regulated by USDA, but may also be used in a variety of other FDA regulated products.

These products can include many consumer products such as dietary supplements, ingredients, cosmetics, and certain drugs. Consequently there are many multiple routes by which consumers could potential be exposed to bovine neurological tissues. It is also relevant to point out at this time that although there is currently no evidence that BSE is present in the United States, FDA is unaware of any practical means by which it could detect the BSE agent in the above listed foods or products even if the agent were present in this country. And so FDA must consider other

means other than routine testing to protect the U.S. consumers from exposure to BSE agent, or the potential exposure.

There are two main laws that FDA can use to protect the public health. The first is the Public Health Services Act, which enables FDA to promulgate regulations to prevent the introduction and transmission or spread of a communicable human disease. The second, and the one that is the more widely used law, is the Federal Food, Drug, and Cosmetic Act, and this law allows, enables FDA to insure the safety of products that it regulates by acting upon products that are known to have safety problems.

In contrast, FDA's sister agency, USDA's Food Safety and Inspection Service, employs a different set of laws, and that is the Meat and Poultry Inspection Act, to insure that the safety of products it regulates, which are shown on this slide, are also safe. Obviously many of the products regulated by FDA begin as USDA regulated products. For this reason FDA believed that it was important for the committee to hear from an expert on meat inspection and slaughtering procedures from that agency if it was to arrive at informed opinions and decisions.

We have asked a guest speaker, Dr. Bill James, who is in the Office of Public Health and Science at the Food Safety and Inspection Service, to come and talk to you about

specifics of meat slaughtering and neurological tissues, and Dr. James will provide a short summary of beef slaughtering and the ways by which neurological tissues might get into human products.

Agenda Item: Opportunities for Preventing Contamination of Edible Products in a Slaughter Plant with the BSE Agent

DR. JAMES: Well good morning. I'd like to invite you all for, thank you for inviting me to speak today. And this morning I would like to give you an overview of USDA efforts to prevent the introduction of BSE into the U.S., and more specifically the efforts of the Food Safety and Inspection Service in preventing potential exposure to the BSE agent.

As you all know, BSE was first diagnosed in 1986 in the United Kingdom, and since then it has been confirmed in native born cattle in a number of other European countries, and then most recently of course in Japan. The disease is most likely spread by feeding rendered material from cattle infected with BSE to other cattle in the form of meat and bone meal. Worldwide more than 178,000 cases of BSE have been detected since the disease was first diagnosed, with over 99 percent of these cases reported in the U.K.

Now to prevent BSE from entering the United

States, the Animal and Plant Health Inspection Service has restricted the importation of live ruminants and certain ruminant products from countries where BSE is known to exist. In 1989 APHIS banned the importation of all ruminants and restricted the importation of certain cattle products from the United Kingdom. And as of 1997 APHIS prohibited the important of live ruminants and most ruminant products from all of Europe. This action was taken in 1997 because several other countries reported their first cases of BSE in native born cattle, and this was evidence that the European countries had high BSE risk factors and less than adequate surveillance.

And then in September of this year we halted imports from Japan. These decisions were made to protect human and animal health and to shield the safety and integrity of our food supply.

Now in the U.S. almost 17,000 brain samples now have been tested since 1990, and so far no case of BSE has been detected in the U.S. For each of the last six years the rate of surveillance for BSE in the United States has been approximately double the requirements of the International Office of Epizootics standards, and in the last couple of years the number of brains examined have been approximately five times the OIE standard. USDA is continuing to increase the number of brains sampled each

year.

Now the USDA policy in regard to BSE I believe to data has been proactive. In addition to the measures that USDA has already implemented to prevent BSE, the Food Safety and Inspection Service specifically is considering implementing additional measures to further minimize human exposure to materials from cattle that could potentially contain the BSE agent. The measures that FSIS may implement target the materials of cattle that studies have identified as the most likely to contain the BSE agent if an animal is infected with BSE.

Once it is available FSIS will also use the results of the risk assessment on BSE by the Harvard University Center for Risk Analysis to determine which measures would be the most effective at reducing the risk of potential human exposure to the BSE agent.

Now the Harvard Risk Assessment was inaugurated in 1998. USDA entered into a cooperative agreement with Harvard University to conduct an analysis and evaluation of the Department's current measures to prevent BSE. The risk assessment will review current scientific information related to BSE and identify additional measures that could be taken to prevent human and animal exposure in the U.S. They will do this by assessing different pathways by which the agent could enter the country and the most likely

scenarios for human exposure to CNS material that could contain the agent if it were here.

Let's talk for a moment about anti-mortem inspection. Anti-mortem inspection is conducted of animals before slaughter, that's a no-brainer. Among the things inspection personnel look for are signs of central nervous system disorders. Animals showing signs of central nervous system or CNS diseases are condemned. This procedure is conducted with vigilance to prevent an animal with BSE or any other CNS disease from entering the human food chain.

From 1999 and in 2000 over 79 million cattle were slaughtered in the U.S. Of this number 132 cattle were condemned for CNS signs in 1999 and 152 cattle were condemned for CNS signs in 2000. Now let's take just a minute and talk about downer cattle. Downer cattle, that is a colloquialism, are cattle that cannot rise from a recumbent position. This might be associated with a physical injury, it could be associated with a metabolic condition, could have a variety of different reasons why cattle cannot rise. Downer cattle are designated as suspect animals, they are official USDA suspects, and they must undergo an examination by an FSIS veterinarian to determine if they should be eligible for slaughter. Those that pass anti-mortem inspection are slaughtered and receive special attention by inspection personnel at post-mortem inspection.

If the animal passes post-mortem inspection, the meat and meat products from such cattle may be used for human food.

Now while the Animal and Plant Health Inspection Service, APHIS, has always tested downer animals as part of the USDA testing program, because European surveillance data show that downer cattle are among the cattle most likely to be infected with BSE, APHIS has increased the number of downer cattle that it is testing for the disease. FSIS contacts APHIS when we have an animal that fits the profile, and that is an animal that is down, especially animals that show signs of CNS disease, greater than 20 months of age. And then APHIS will send someone out to collect those brains.

I'm going to talk about the slaughter process for a moment now. During the slaughtering procedures there are some processes which are conducted in which contamination of edible products can occur, with CNS material of course. Now I am going to cover four of these for you. These processes are stunning, dehorning, carcass splitting, and we are going to talk for a moment about meat recovery systems.

Alright stunning. Animals that pass anti-mortem inspection are stunned before slaughter to render them insensible to pain. This is a requirement of the Humane Slaughter Act. The most common method of stunning cattle is stunning with a penetrating captive bolt gun, that is a gun

that can be actuated either by a powder cartridge or perhaps it is air actuated. A rod enters the skull, penetrating the skull, and the animal is stunned in that fashion.

Until recently captive bolt stunning that injects compressed air into the cranium was commonly used to disrupt the brain structure and induce total and prolonged unconsciousness, which is intended to insure that cattle are slaughtered in a humane manner. However, air injection stunning has been shown to force large pieces of brain, micro-emboli, into the circulatory system of stunned cattle. These brain micro-emboli lodge in edible tissues, for example the liver.

Studies have shown that when correctly used, captive bolt stunning without air injection also induces total and prolonged unconsciousness and can be used to effectively slaughter cattle humanely without creating the micro-emboli in the circulatory system. The industry is aware of this and an informal survey of common stunning practices by the industry has revealed that virtually all plants have stopped using air injection stunning at this time. I say virtually all, I won't say absolutely all. This is a large country and we have a lot of plants.

Let's talk for a moment about dehorning. FSIS requires that the horns of horned cattle be removed. This is primarily a sanitation feature. Sometimes this process

unintentionally exposes the brains of the animals when a mechanical device is used to remove the horns. This doesn't happen routinely, but it happens on occasion. And although the potential for contamination of head meat with brain material in this way is considered slight, it need not occur if care is taken when horns are removed. When the horns are normally removed it will expose the frontal sinus of the cattle skull. It will not expose the brain unless a wider area of skull is removed when the horn is removed.

Now in rare instances the skulls of cattle are intentionally split to remove materials contained within the cranial cavity, such as pituitary gland, and this is for non-human food purposes. However, in these instances the head meat is removed before the skull is split, so the head meat would not be contaminated by this route.

Carcass splitting, we are moving down the line now, the animal is being subjected to continuing processes in the overall process of changing animals into edible product. Carcass splitting, on the slaughter line the vertebral column is split using a power saw, something like a band saw. Spinal cord tissue can be transferred to meat during this process. During this process the saw must be effectively rinsed between carcasses and the saws do have a built in rinsing mechanism. If they were not rinsed between carcasses you would run the risk of transferring spinal cord

tissue between carcasses, from one carcass to the next.

Now I am using the term transfer here rather than contamination, although you might hear me say the word contamination again, because I need to illustrate this fact. CNS is edible material and to date, historically, we have not had a reason prior to the introduction of BSE to consider it to be inedible material. Some people like CNS material. They go out of their way to find it so they can eat it. Brains and spinal cord, when collected in a sanitary fashion from inspected and passed carcasses, are wholesome and they may be sold for human consumption if properly labeled.

We'll move on to meat recovery systems. Now studies have identified bovine spinal cord and dorsal root ganglia as two of the materials that are likely to contain the BSE agent in BSE infected cattle. Dorsal root ganglia, DRG, are expansions of the sensory branches of the nerves near the spinal column that are surrounded by the bones of the vertebral column. Consumption of meat or meat products produced using meat recovery systems is one of the most likely pathways by which humans could potentially be exposed to the BSE agent if it were in the cattle herd.

Now recovery systems that use pressure to separate beef meat or meat products from the bone include both advanced meat recovery systems or AMR systems and recovery

systems used to produce mechanically separated beef. AMR systems separate meat from bone by shaving, pressing, scraping the muscle tissue from the bone surface, resulting in product that is comparable to meat derived from hand deboning. Inspection personnel visibly check bones going into these meat recovery systems at random for the presence of spinal cords, to insure that the spinal cords have been removed from the vertebra that go into this process.

When the skeletal muscle is separated from the bones using AMR systems, under appropriate controls, the resulting product is meat, and it may be labeled so. Meat produced using AMR systems is commonly found in ground beef or hamburger, sausage, things of that nature. Mechanically separated beef covers product manufactured by machinery that operates on the principle of differing resistance of hard bone and soft tissue to passage through small openings in the machine such as sieves or screens.

The consistency of mechanically separated beef and its content of bone and certain minerals as well as muscle tissue are materially different from those of meat, and thus, although mechanically separated beef may be used as an ingredient in meat food products, it is not meat and cannot be labeled as such.

Establishments that produce boneless meat using AMR systems remove the spinal cord before the bones of the

vertebral column enter the system. However, sometimes the spinal cord may not be completely removed, especially when a carcass is mis-split. The American Meat Institute has implemented good manufacturing practices for its members to follow to minimize the potential for this occurrence, but this is an occurrence which can happen from time to time.

Bones from the vertebral column, besides possibly containing the spinal cord, will have the dorsal root ganglia associated with them. When bones from the vertebral column are used as a source material in AMR systems or systems that produce mechanically separated beef, it is possible for these materials to be incorporated into the end product, thereby exposing people to materials that could potentially have the BSE agent in the U.S. if BSE were to show up in the U.S.

FSIS is currently finalizing the proposed rule on AMR systems that clarifies the prohibitions on the incorporation of CNS tissue, including spinal cord and DRG in meat produced using AMR systems.

USDA policies to date I believe have been proactive, they have been preventive. The Food Safety and Inspection Service and the Animal and Plant Health Inspection Service will continue our close collaboration with all stakeholders. We'll also continue to monitor and assess ongoing events and research findings regarding

spongiform encephalopathies at home and abroad. We will revise our policies as warranted. We'll take appropriate preventive actions in response to the growing knowledge concerning BSEs.

Now this is the sum of my presentation. I don't know if for some of you it has been too elementary, and for some of you it may have been, left you with many questions. I would be very happy to answer any technical questions that you have.

Agenda Item: Committee Discussion

DR. BOLTON: Thank you Dr. James. I'm sure there are going to be many question (laughter), so we have plenty of time so we will launch right into them. Yes Dean?

DR. CLIVER: At a previous meeting when this process was described perfunctorily we were told that when the spinal cord, for example, was separated from the carcass, that it was put in a container and stained. This doesn't sound compatible with the definition of CNS tissue as food. That was a question by the way, sorry (laughter).

DR. JAMES: So does it sound compatible, okay, yes. Any material that is condemned is placed in inedible containers and denatured by some fashion, a dye, charcoal, something of that nature. Very few spinal cords in the U.S. are harvested for human consumption, so that is the typical fate of a spinal cord. However, if the spinal cord is

harvested in a sanitary fashion from an inspected and passed carcass, it may be used as an edible product, seldom is, but may be.

DR. ROOS: I know that the U.K. has implemented a number of procedures in order to enhance safety during slaughter and prevent contamination of central nervous system tissue, and I wondered whether you were familiar with that, and whether you could comment with respect to how our practices differ from their's, especially with respect to the issue of central nervous system contamination.

DR. JAMES: Yes, I can make perhaps a couple of points there that might be useful to the committee. Of course as we all know, BSE originated in the U.K. as far as we know. They have had a terrible epizootic in the U.K. associated with BSE. The U.K. is the home of the vast majority of the human cases of variant CJD. And so it makes perfect sense that the U.K. would take measures that other countries have been slower to adopt.

Among the things that the U.K. has done is prohibited the saving of cheek meat or head meat of any sort from their cattle. They are concerned about contamination of that head meat with the brain material. Another thing that the U.K. has done is eliminate the use of, I believe they make reference to it as advanced meat recovery product. They don't allow product of that nature to be produced,

especially using vertebral columns.

It is important to, it is my understanding, however, that the product that in the U.S. is referred to as advanced meat recover product, is not the same product that went by that name out of the U.K. In the U.K. their system produced a product that was more like our mechanically separated beef, and so although they had the same name, they weren't the same product.

Other countries have been slower to adopt those measures, not because they have, they are facing a different epizootic situation in those countries. Does that answer your question? So specifically regarding brain and spinal cord, the two chief sources of, well, essentially all CNS material.

DR. ROOS: How about carcass splitting, and the sequence with respect to removal of the spinal cord or adjacent areas?

DR. JAMES: The carcasses in Britain to my knowledge are processed the same way they are in the U.S. in regard to the splitting of the carcass, it is the same thing. They are split on the kill floor and the spinal cord removed at that point. And so in that respect I'm not aware of any differences between the way they are handled in the U.K. and the U.S.

DR. ROOS: One last thing with stunning. Is there

use of bolts and stunning?

DR. JAMES: I'm not aware, well there are other means that can be used in the U.S. also, but in the U.K. they use a similar means to stun the animal, and since they are not saving any head meat, they don't think that that poses any risk at all.

DR. BOLTON: I want to welcome our former Chair, Dr. Brown. I saw that he has a question. Paul? Wake up over there Paul (laughter).

DR. BROWN: Believe it or not I am awake. Granted the U.S. has close to a zero likelihood of seeing BSE if precautions are followed, other European countries of course felt the same way before they had BSE, and is there any reason for example why the slaughter houses in this country could not, as they do in Europe, although they don't in England, remove the spinal column, that is make two cuts and not one cut. Not the spinal column, I should say the vertebral column. There's no way, even with advanced meat recovery, that central nervous system tissue and its para-spinal ganglia can be guaranteed to be removed from a carcass short of not using the vertebral tissue, the vertebral column. And in this press that is used to squish out recovered meat there is no possibility to guarantee, short of removing the vertebral column, that some component of either residual spinal cord or para-spinal ganglia can

find its way into mechanically recovered meat. So it would seem to me that if it were not terribly difficult to do, and apparently it is not because most of the European Union countries are doing it, that this would not be a bad thing for the slaughter house business to do.

And the second thing of course is simply to stop using any kind of meat pudding which goes under the legal definition of meat, which was certainly the villain in Europe, and if we ever got BSE, would almost certainly be the villain in this country as well.

DR. JAMES: I knew there was a lot there. Let me see where to begin. Technically it would be possible to remove the vertebral columns so that it is not utilized in, meat immediately adjacent to the vertebral is not utilized in any human food product. However, some of the best quality and most expensive meats come from that area, and removal of the vertebral column in a fashion such as making two cuts rather than the one as you described would be a very costly approach. I believe it could be done, but it is a costly approach.

And you are correct in that if an excellent job is done in removing spinal cord from vertebral column before it goes into an advanced meat recovery system, you still are going to find dorsal root ganglia in the meat, you'll find some degree of that. That will be a difficult thing to

eliminate completely, and certainly in the mechanically separated product you would find that.

There may have been one or two other things you wanted me to comment on there, and I've lost them.

DR. BROWN: No, I think that, I mean that is obviously the consideration, expense and cost not to take out the vertebral column and simply not use it, and presumably that is an expense that is being absorbed by the European community countries at the moment. But the alternative would be simply to cease using advanced meat recovery products, which would also be costly. But it seems to me that unless one of these two approaches is taken, then should be ever get BSE in this country, heads will roll because this was not done.

DR. JAMES: I would like to assure everyone in this room that USDA Food Safety and Inspection Service is acutely aware of the potential disaster associated with the introduction of BSE into the U.S. We have monitored very closely the situation in the U.K., the rest of Europe, the situation that is evolving in Japan. We are actively considering a variety of other measures that could be taken, but it is premature today for me to discuss those because we need to wait for the Harvard Risk Assessment to be released in order to improve our evaluation of the current situation in the U.S., and to take advantage of the information in

that risk assessment before proposing any other rules.

DR. BOLTON: Peter?

DR. LURIE: Well we'll start with that then. The Harvard Risk Assessment is something we have been promised for oh at least six months now. Can you tell us what is going on?

DR. JAMES: I can tell you that we hope to have it released soon (laughter).

DR. LURIE: Sounds like a, well okay, thanks for that (laughter). The second question is an information one first at least. On these advanced meat recovery, mechanically separated product, must they be obtained from the para-vertebral region, I mean can they be taken of long bones?

DR. JAMES: Yes, and they are. The vertebral column, the vertebra are just other bones from which the products are derived.

DR. LURIE: So I mean just a modification then on what Paul is saying is I suppose as much as many of us find neither of these products to bear much resemblance to meat, no matter how it is that the USDA happens to regulate them, from a strictly BSE perspective, then all one would need to ban, I suppose, is not AMR or mechanically separated product, but their being sourced from para-vertebral regions. Is that right Paul?

DR. BROWN: Yes, and I was told also by the folks in Europe that long bones really, at least there, are too hard for the press and typically long bones are not used in the process of advanced meat recovery. It is shoulder blades, vertebral column, and pelvis.

DR. JAMES: I don't know that that is the case here in the U.S. I think some of the bones are reduced in size before they go into the machine. I am going to see if my colleague, Dr. Dan Engeljohn, can shed a little bit more light on that.

DR. ENGELJOHN: Good morning. My name is Dan Engeljohn. I'm with USDA. Within the U.S. manufacturing operations a variety of bones are used. We do have long bones that are used, and as Dr. James mentioned, many of the operations do cut those bones into smaller pieces and press those. So there's a variety of systems that are used. But the split vertebral column is the one that is preferred to be used, simply because it is in fact split in half and the yield from those bones are considerably higher than they would be from the longer bones that would have less meat that could be recovered from them.

DR. BOLTON: But on the other hand, what is the total amount of meat that is recovered in a mechanically recovered meat system, as a proportion of the entire meat from the carcass? This must be a very small percentage of

product, and yet it contains by far and way most of the high risk material. I mean most of the infectivity is going to be associated either with the brain, the brain stem, or the spinal cord. It seems to me the point of diminishing returns to try to recover that last bit of meat, if there is infectivity in any mammal that is where it will reside.

DR. ENGELJOHN: I could respond by saying that, as you mentioned, the yield is considerably less than the total front of the whole carcass. It would be less than five percent, from the carcass, would be an expected amount that could be there. And we would have more exact numbers for that that we would be coming out with once the risk assessment is issued and we are able to provide more information.

I would just like to add that on the discussion of the use of the vertebral column, if you don't use it, if it is not used for the advanced recovery system of pressing the materials from those bones, then those bones go into edible rendering and are used for other purposes for which the materials are rendered from them. So by banning, in your considerations of not using the vertebral column at all, then the decision would need to be as to whether or not that material would be edible and can go into other products such as rendering for beef soups, beef stocks, and the like.

DR. LURIE: Actually, to help quantify the answer

to your question David, in a packet was this document from FSIS, this one over here, which I guess estimates one to one and a half pounds more beef from a carcass than from hand deboning operations. So how much meat do we get from a carcass ordinarily? Are we talking about a few hundred pounds?

DR. BOLTON: I would guess so, yes.

DR. LURIE: Well how much, a thousand pounds?

DR. JAMES: No, less than a thousand pounds. I should be able to answer that off the top of my head, but all of a sudden I find myself drawing a blank. I can return with the answer to that question at a later date or get it to the committee, but it would be less than a thousand pounds, it would be at least several hundred.

DR. BOLTON: I think the steers that slaughter around what, 1,200 pounds maybe, 1,200 to 1,500 pounds, and so it is going to be certainly much less than that, it might be 400.

DR. LURIE: So the answer to your question is considerably under one percent is the answer, right, is that a fair statement then?

DR. BROWN: Yes, it would also be, one thing that it would be nice to have, a number, and I don't know if anybody has ever done this, but you should be able to use some sort of enzyme assay to determine how much actual

muscle tissue is in mechanically recovered meat. I mean the pudding that comes out surely must have almost no muscle in it by the time it gets to that, and I would really like to know a number as to how much muscle tissue, what percentage of mechanically recovered meat is meat. Anybody in the room answer that question?

DR. JAMES: Product that results from the advanced meat recovery system is meat. The majority, almost all of it, is muscle tissue.

DR. LURIE: What you mean is that the material recovered by advanced meat recovery is regulated by USDA as meat, that's what you mean, right?

DR. JAMES: No, I mean it is muscle tissue. The definition of meat is muscle tissue.

DR. LURIE: Yes, but we know it has got some CNS in it, right? I mean there's studies that FSIS itself has done that have shown the presence of CNS tissue in AMR material, right?

DR. JAMES: That's correct. The meat, although it is muscle tissue, it is recognized that there will be other materials in their natural proportions, and that are not necessarily strayed skeletal muscle.

DR. BROWN: Well it surely must be tendons and ligaments and bone marrow if you are crushing the vertebral column. I find it very difficult to believe that most of

the tissue in mechanically recovered meat pudding is muscle.

DR. BOLTON: Well at this point that may be something that is going to have to be looked at or I don't think we are going to have the factual data here to answer that. Let's get Dean in here.

DR. CLIVER: Well first of all we are doing some apples and oranges comparisons here. Slaughter weight animals the majority of the animals that were tabulated there are going to average about 1,000 pounds live weight. Dressing percentages may be 600, 60 percent, 50 percent, somewhere in there. Take out the bones well you are talking about maybe 400, maximum 500 pounds of meat. I think that is fairly straight forward.

We are, it seems to me, needlessly blurring the distinction between very well defined advanced meat recovery systems versus mechanical recovery systems.

DR. JAMES: Mechanically separated products, yes.

DR. CLIVER: Mechanically separated product, okay. Advanced meat recovery does not entail grinding up bones. Now as far as what proportion, well, the pound, pound and a half extra per carcass by AMR, this is being compared to hand trimming, which is a much more labor intensive procedures, and yes you could go back to that, but to some extent the conservation of that edible portion is going to be way more expensive if you go back to hand trimming. So

AMR is a different thing than mechanical separation. It does not entail grinding of bones.

Also I heard stated as fact that the European Union is doing this two-cut carcass splitting, but I didn't hear that confirmed by our speaker, who says that FSIS is in close touch with what is going on in Europe as well as the U.K. This, I would like to have that clarified.

My lab is involved in comparing two commercial test kits right now for the detection of CNS in meat, beef, and there are commercial test kits for this purpose. If we get away from the question of what proportion of our AMR product is muscle and go back to would we really like not to have CNS tissue there, well there are already commercial test kits that are being marketed for that purpose. Whether they really are as effective as their manufacturer's say remains to be seen, but that's what we are doing.

Finally, again to the speaker, I teach a course on the hazard analysis critical control points system of food safety at the University of California Davis, and I've just come back from Japan where last week they put in 100 percent testing of brains of all slaughter bovine animals, including veal calves. That strikes me as overkill, but I would like to know are we in a position as we process carcasses in the United States to designate critical control points that should there be an introduction or discovery of BSE here,

would get us out of the mold of having to test all those brains. It just strikes me as a terrible waste of resources. Could this be a critical control point that we would have faith in? Sorry to go on so long.

DR. JAMES: The USDA as a department has a BSE emergency response plan which is a public document available on the web. Furthermore, FSIS is prepared to take appropriate measures is a case of BSE were diagnosed tomorrow. We prefer to not, of course we prefer never to have to be put in that position, but we are not prepared to put forth as public policy for public discussion recommendations for what FSIS might do beyond what it is doing at the moment, until we have had a chance to study the Harvard risk assessment.

DR. BOLTON: Well let's go back. I think Dr. Cliver was asking one specific question and that was what is your knowledge or the FSIS knowledge of the carcass splitting method in either the E.U. or the U.K.?

DR. JAMES: To my knowledge, and having discussed this with various people, the carcass splitting procedures in the U.K. and Europe on the kill floor are the same as those being employed in the U.S. I will confirm that and provide that information to this advisory committee.

DR. BOLTON: Just before we go further, I want to broaden this issue a little bit less we become completely

consumed by mechanically recovered meat. As I see it there are two issues that we need to consider and address. One is the risk associated with unintentional transfer, if you will, or contamination of CNS tissue in meat products, and the second is really the intentional introduction of CNS tissue to humans via food, either by consumption of brain or other CNS tissues which are allowed, or their direct introduction into dietary supplements and those kinds of products.

And so I would like to broaden the discussion to include those areas, because we can debate all day about whether or not the mechanically recovered meat is a problem, but if people are going out and eating brains or unknowingly eating brain in a dietary supplement, we are sort of missing half of the battle. Lisa, do you have a question?

DR. FERGUSON: Well actually I was just going to elaborate a bit more perhaps and try to help Bill out there with an answer. And our understanding from APHIS as you pointed is the same as Bill's, that primarily in Europe they are still using the same process that we are, which is splitting the carcass direct down the middle. There might be some plants that are using like a V-type saw, but primarily it is a split.

And I would also like to make the point that throughout most of the community, now the U.K. is a separate

case, but throughout most of the community it has only been fairly recently that they have prohibited the use of mechanically separated meat derived from the vertebral column.

DR. BOLTON: I wonder though if they wished they had started earlier.

DR. FERGUSON: Oh I suspect they do (laughter).

DR. BOLTON: So let us not fall into the trap of waiting too late.

DR. JAMES: If I may just interject very quickly. We certainly appreciate that point. As I mentioned, we are very much aware of the dangers of waiting too long, which is why we are very expectantly looking forward to the release of the risk assessment and are prepared to act as soon as is practical after that is released with putting forward some proposals.

DR. DE ARMOND: I'm continually asked three questions by journalists, ones that relate to this issue. One has to do with the use of brain CNS material in the United States, and it seems to me from the discussion here, perhaps we are going to have to go to a kind of legislation as we have for seat belts and helmets for motorcyclists and bicyclists, that we proactively say you can't use CNS tissue for food products or any other products derived from bovine because of the possibility that ultimately it can become

infected. But that's an issue that I don't want to get into here. But it seems like we may be heading towards that direction, and in that case then we do have to take the spinal column, the vertebral column out and dispose of it, burn it and not use it at all.

But the other question that relates to that, since we don't have any BSE as far as we know in the U.S., everyone asks what sort of processes do we have in rendering that are different than in Great Britain, that if the disease were introduced here would prevent it from amplifying as it did in Great Britain. And the second part of that, so that rendering, is the rendering the same or different than in Great Britain.

And the second has to do with control of BSE contaminated products coming into the United States. I know there are all these regulations about beef and cattle and big things, but they always ask do we have a leaky sieve, do products go to Venezuela and then come back up here that are infected. And this gets to be complicated because there is at least three or four different, two major agencies and subsets of those agencies that seem to have different controls, and the journalists are confused and I can't answer their questions.

So first of all, let's go to a simple thing. Is the rendering in the United States the same or different

than in Great Britain, that lead to the amplification problem. And then secondly, how are we absolutely assured that nothing is going to come in from Europe or some other country, South American or wherever, that potentially has BSE in it.

DR. JAMES: Well the first part of that question I would have to make reference to FDA regarding rendering or, FSIS does not oversee, doesn't have regulatory authority over that area, and I wouldn't want to begin to try to answer that as an expert.

DR. DE ARMOND: Well that is one of the problems that I am being, that is being addressed to me, how come there are so many different agencies dealing with the same problem and not working hand in hand. I'm telling you they are very upset about this.

DR. FERGUSON: I think I can answer the rendering question, although I would make the point that, you know, APHIS is not necessarily the primary authority for rendering, for regulating the rendering process in the U.S., but just to answer the direct question. Our rendering processes in the U.S. are essentially the same as they were in the U.K. in the 80s. At this point in time in Europe, rendering processes, at least according to regulations, have supposedly changed and now supposedly in Europe they are all using a batch system, 133 degrees CST vice pressure for 20

minutes. We are not using that system in the U.S. Essentially there's hardly any batch renderers in the U.S. at this point in time. So we are using the same systems that the U.K. was using at that point in time.

DR. DE ARMOND: So if contaminated, if a BSE brain or spinal cord were introduced into our rendering system because the spinal column is thrown in there for rendering, there is a potential to amplify the disorder.

DR. FERGUSON: Yes there is, and I think when the Harvard assessment comes out a lot of this will be perhaps explained a bit clearer and it will, at least I always find these things easier to look at on paper. But our system, and really the department recognizes these facts, that we did import live cattle from the U.K. up until 1989, and some of those animals could have gotten into our system, and at that point in time our rendering systems would have, while rendering can decrease the agent somewhat, I mean even the 133 degrees C doesn't completely get rid of the agent, but most rendering systems will decrease the level of the agent somewhat.

But our systems, we would have been in the same boat as the U.K. and up until August 1997 we did not have a ruminant feed ban in place, so we did have a chance for the agent to get here, to be recycled, and to be feed back to cattle. This is one reason why we at APHIS have tried to

maintain a fairly active surveillance system for so long, is because we recognize that fact.

Now I would also like to point out that, you know, if we are assuming that an infected animal was the primary source of the introduction of the agent, that would have happened in the early 90s if we are counting on like a five year incubation cycle. We should be at about the peak, and our surveillance at this point in time is at the peak and we still have yet to see it.

DR. BOLTON: I would like to continue this discussion but I understand that Dr. James may have to leave, is that right, between 10 and 10:30?

DR. JAMES: Approximately 10:30 yes.

DR. BOLTON: Okay, so what I would like to do, our agenda actually calls for Dr. Brackett to present the questions for the committee, and that will take about 10 minutes according to the agenda, and then lets then resume this discussion with Dr. James here, so we can sort of maximize the scope, because I think considering the questions may perhaps focus us a little better on the discussion, or maybe it will diffuse us, I'm not sure, but let's move ahead with Dr. Brackett and the questions. And Dr. James, you'll stay here until, well immediately we'll resume the discussion. Thank you. Dr. Brackett.

Agenda Item: Presentation of Questions to the

Committee

DR. BRACKETT: Thank you Mr. Chairman. I would like to discuss the questions now too, and sort of go through them as an overview. But before doing so I would like to emphasize that in the event that the committee, that it appears to the committee that there is insufficient scientific knowledge to make some concrete judgment, we are still interested in hearing, and I think that many should feel free to offer their best judgment based on what they do know, because this is sort of a moving scientific field, or simply choose to say that there is too little data to even make a statement about that, and that is acceptable as well.

The other thing I would like to mention is that we would like to focus specifically on our FDA regulative products and specifically to what Dr. Bolton had mentioned about those products that have intentional addition of CNS tissue. We would rather not go into the issues of USDA policy during this meeting.

Okay, so I'll go on to the questions. The first question we have is what is the public health risk to consumers that would warrant consideration of prohibiting the sale of bovine brain and products containing brain for human use?

Secondly, Is there a consistent and appreciable difference in infectivity of various sections or areas of

the bovine brain, and if so, what are the differences in relative degrees of infectivity of these areas?

And three, are there any bovine neurological tissues that, if used in consumer products, and these are such as regular foods, dietary supplements, cosmetics, and certain drugs, would also pose a significant health hazard? If so, what are the differences in the relative degrees of infectivity of these tissues?

Four, question four, what physical, chemical, or biological factors of tissues, physical characteristics of the tissues themselves, or of the processes should FDA consider in reviewing procedures that may have the ability to reduce infectivity of bovine neurological tissues and products containing these tissues?

Next, what tests are available to ascertain changes in infectivity in products containing bovine neurological tissues as a result of the processing?

Question six, what level of reduction in infectivity is necessary to consider products containing bovine neurological tissues non-infective or "safe" for human use?

At this point I will turn the section back to our Chair for discussion of these points. As I said, we are interested in hearing, getting as much information and this is a long list of questions, but we are interested in

learning as much about this topic as we can. Thanks.

Agenda Item: Committee Discussion and Votes

DR. BOLTON: Thank you Dr. Brackett. I think we could fairly quickly deal with the first two questions before we again begin to broaden our discussion. The first question, what is the public health risk to consumers that would warrant consideration of prohibiting the sale of bovine brain and products containing brain for human use. I would suggest that the presence of undiagnosed or pre-clinical BSE in U.S. cattle could certainly be the public health risk to consumers that would warrant that. It is a big step and perhaps a large and controversial statement to move down that road.

However, I guess I view this in two ways. I am very comfortable with our freedoms in this country, that if somebody wants to go out and knowingly purchase bovine brain and eat it, I guess that is their business. I'm uncomfortable with somebody buying hamburger thinking it is meat and finding out that it has some CNS tissue in it, and I'm uncomfortable with somebody buying a dietary supplement unknowingly that contains brain or CNS material that may or may not be labeled so that the consumer would understand the risks that they are taking.

So I would open that up for discussion, and secondly, the question is there a consistent and appreciable

difference in infectivity in various sections or areas of bovine brain, I believe that the studies indicate yes, that there are differences, but I'm not sure how good the quantification is, so somebody else may have to remind me of that. Steve, you may know, or Paul you may remember.

So I think those two questions are not particularly controversial, but let's open these up to committee discussion.

DR. GAMBETTI: I think a very important point to be able really to discuss the first question is to discuss an issue that at least has not been discussed so far with Dr. James. That is the surveillance. In other words, how, in order to really assess the risk on consuming certain ruminant product, I would like to know what is the current state of surveillance on BSE in the United States.

DR. BOLTON: Lisa, can you speak to that?

DR. FERGUSON: Yes I can, and actually I have my computer with me and I think I have a presentation that has some maps that would show our recent surveillance if that would be helpful.

DR. BOLTON: I think that would be most helpful. If we want to continue discussion while you can set that up, that would be an added bonus. Steve?

DR. DE ARMOND: I would just like to reiterate what you said. I believe that we over-regulate things to

begin with in some sense, and I would prefer that we have the freedom to eat brain if we want to, and it has not been a problem until this BSE problem arose artificially in a sense in Great Britain. And as long as we have the surveillance in place that could guarantee that our meat products or our beef is not infective, I would be very happy with that. If the surveillance doesn't work and if it is a false hope, then we have to consider banning the CNS. But I think it certainly should be able to work. We have very competent people in these areas.

DR. LURIE: Well you know, it is well and good to appeal to American freedoms and the like, but when one looks at it from the consumer perspective -

PARTICIPANT: The other one is freedom.

DR.LURIE: But one can only have freedom to make a choice if one is adequately informed, correct? So then the question from the consumer perspective becomes how well are people informed about the risks. So let's take the materials in turn. The first material is mechanically separated product, which is not labeled as meat it is true. My guess is that the average American, if they have ever noticed that phrase on any product, has not automatically leaped to the conclusion that that, among other things, implies may include neurol tissue. I rather suspect that it doesn't mean that to them.

But if for mechanically separated product, if they felt that is what it meant, they certainly don't think that when they look at advanced meat recovery material, which can be labeled as meat. So in that case they have absolutely no reason to believe, so that are clearly not informed in that case.

The third is with respect to the consumption of brain itself, again, you know I'm not in the usual position of purchasing brain for consumption, but I guess I would like to know if there is anything about brain when it is sold that, you know, that comes with a little label suggesting this may contain infective material from the CNS system. So I rather suspect it doesn't.

So again appealing to American freedoms is fine if people are informed, but what is the evidence that they are.

DR. BOLTON: Yes, I would like to echo that and in fact to compare the packet information on for example an injectable drug that might contain bovine serum albumin and the risks that are listed there versus brain which you might buy at the butcher shop, which would have of course no labeling whatsoever. And another issue is if something -

DR. DE ARMOND: Except USDA certified.

DR. LURIE: Yes, USDA certified that it may contain brain, right?

DR. BOLTON: And the other issue is even a product

properly labeled, let's say a supplement that might have bovine thalamus in it, how many consumers would understand what bovine thalamus is and what risk that might contain. Additional discussion. Dean?

DR. CLIVER: Assuming Lisa is not set up yet, because I am very keen to see what she has to present, my thought is that we are in an ethical box by being told that we're constrained only to consider FDA's jurisdiction here. There are gradations of risk in everything that we've had to confront, and if brain and spinal cord can still be offered as food fit for human consumption through FSIS, and we take the action that potential traces of central nervous system tissue in some other product are unacceptable from a risk standpoint, it is going to be very hard to defend that logically over the long pull.

I understand the jurisdictional problems here, but all the same, if we want to say there shouldn't be brain in a nutritional supplement, at some point we maybe have to say that brain should seriously be considered as unfit for human consumption as a primary edible.

DR. BOLTON: I agree that is certainly a consideration. I think going back to Peter's point though, it is in one sense an issue of informing the consumer as to exactly what it is that they are getting. Paul you were first?

DR. BROWN: With respect to the exact wording of the questions, this one is focused and limited to brain. So if we are going to answer the questions, probably we should just stick to brain if you want to answer this particular question. And as near as I can tell people eat brain for only two reasons. One they like it, I mean as a food, and two it is fed occasionally to people to increase intelligence. Either way it is their choice. I'm not sure how you would inform people a brain can after all be bacterially contaminated as well, like anything else.

So I don't expect that you would want to put a disclaimer on, you know, brains in a butcher shop, this product may contain BSE or may be infected with bacteria or da dah da dah. I would say that you summarized question one and the answer to it perfectly. And question two, yes there are differences in infectivity, but those differences are to a large measure unpredictable and to even consider thinking of a hierarchy of risk according to area of the brain would be just dumb.

DR. DE ARMOND: Can I echo that also, because there are hot spots in the medulla where there is very high infectivity, but in a bovine brain we assume every part of the brain and spinal cord is infective. It is just that there is a higher tighter in some areas.

DR. STRONCEK: You know I guess we, the country

tends to regulate cigarettes as saying that there are certain risks and consumers can take that risk if they choose, but blood we don't really regulate it that way. We test it extremely well and we make it, we really make sure it is very safe. I think people would expect food to be the same way. They want food regulated as blood, not cigarettes, saying oh sure you can go ahead and eat brain, but you may get, you know, some disease from it. I think they would expect that it is very safe or it is tested to insure it is safe.

And I'm not sure doing this surveillance, even if we do a lot of surveillance, cultures of cattle brain at the time of slaughter, it might be too late by the time we pick up that BSE is in the country. So it may be more prudent just not, to ban the use of brain from food products.

DR. BOLTON: Ray, and then Lisa is ready.

DR. ROOS: I think it would be a bad idea to have little warning inserts every time you want to buy a hamburger or a piece of beef, in the sense that, you know, if you've got a pork chop there isn't something that says you may get trichinosis, and if you buy fish it doesn't say that you may get a parasite or a worm. And so I think to me that would be a bad precedent here. I think the public needs to be informed and educated about risks, but I think we are going to go down, start a ball rolling here with

respect to consumers about health hazards, that if we were to require that information at a butcher store.

DR. LURIE: To respond to that specifically, I mean maybe USDA can help me out here, but it seems to me that just relatively recently I've started to notice showing up on cuts of meat instructions to consumers on how to cook it, how to prepare meat and so forth. So they in fact are, not exactly a precedent, but a largely similar expansion of the kinds of warnings that provide to consumers.

But the second point again is yes, if you buy a brain in a butcher store, you know, it looks like a brain, you know you are getting a brain. The problem is that people don't know what mechanically separated product is and advanced meat recovery, which at least at times contains neurol tissue, is called meat. And I would look at that as mis-labeling in the first place.

DR. ROOS: I agree with that.

DR. BROWN: But this is not brain, this is not brain. The head is off. So if we are still talking brain we can wait, mechanically recovered meat, until later.

DR. BOLTON: I would like to have Lisa present her data on the surveillance at this point.

DR. BRACKETT: Could I say one thing first?

DR. BOLTON: Okay.

DR. BRACKETT: The one thing that I would again

like to reiterate to the committee and really stress is that we are dealing strictly with FDA products, and the USDA products like the ground beef and the mechanically recovered meat should really not be discussed at this time. However, when we are talking about brains, we are not just talking about brains, but realize that these tissues are often used in other products like broths and bullions and those sorts of things, and so those we do, are considered. Those are FDA regulated products.

DR. BOLTON: Ah. So wait Dr. Brackett, a point of clarification then. You are saying that, for example I guess it was stated earlier that if the vertebral column was removed and not processed through the mechanically recovered meat system, that they could then go into making these bullions and broths if not otherwise restricted. And I assume then brain could also be used?

DR. BRACKETT: Yes.

DR. BOLTON: So we may have the situation where brain and/or spinal column, spinal cord, are going into some cooking process which then produces beef bullion or other similar food products and/or pills like various dietary supplements.

DR. BRACKETT: Exactly. They could be used in other, or they could be further processed and actually end up being an FDA regulated product, that is a separate issue

from that of whole cuts of meat, where you have incidental contamination of tissue.

DR. BOLTON: Okay, so then I would like to definitely refocus the committee onto these products, which to me are perhaps even scarier than the mechanically recovered meat products. Lisa?

DR. FERGUSON: I'll try and just hit the high points because this is a presentation, it is like part of a presentation, so not all of this might be relevant. But we have been doing surveillance for BSE since 1990 and primarily where we are obtaining our samples are from these two points that you see on the screen. Central nervous system cases. As Bill mentioned earlier this morning, any animals that on anti-mortem inspection at slaughter are condemned for central nervous system signs, FSIS calls us and we go out and obtain a sample from that animal. We also do that, we actually do an investigation for an exotic disease on those animals. You see the first note there that says farms. If a farmer has an animal with a non-responsive central nervous system disorder, they can call us and we will again do an exotic disease investigation.

Laboratories. We are working with a system of veterinary diagnostic labs around the United States, where if they have cases of neurological disorders, their pathologists will look at those samples specifically

following MVSL's same protocol for examining them for BSE lesions. So those are kind of three separate points there.

Also on downers, this is really a significant part of our surveillance at this point in time. We've been examining what we call downers, what are called fallen stock in Europe. These are non-ambulatory animals. They can't get up for whatever reason. Many times it is not actually a neurological problem, it is a muscular skeletal problem. There are various things that can cause an animal to be down and not get up.

But I think we are all familiar with Dick Marshall's work with TME and the allegations that were made there, that that was a TSE in cattle that got fed back to mink and on the basis of that research we've incorporated downers in our surveillance since approximately 93 and 94, and what we are doing is there are plants that will routinely slaughter these animals and we go out to these plants and will just obtain samples.

Test methodology, currently, obviously when we started we were just using histopathology. Again 93, 94 we started using immunohistic chemistry. At this point in time at our National Veterinary Services Lab we are trying to run immuno on every sample that we get. Obviously some samples are not amenable to that, but we are essentially doing a hundred percent with immuno. We do have western blood

available to us as a backup.

The rapid tests, we are not currently using those. We have talked with all of those companies. I believe we have the equipment and are starting some evaluation and validation of those processes, but we are not using them at this point in time.

This slide shows a summary total. Now these are cumulative totals of samples that have been looked at, broken by state of origin, since 1990. Through the end of September the grand total was 16,803, right down here in tiny little print. But you look at this and if you are familiar with the cattle population in the U.S., the instant assumption is well are the samples obtained from each state reflective of the population in that state. And the answer is no they are probably not, because animals move around in the U.S. and many animals are not slaughtered in the same state that they were raised. So these numbers reflect where we obtained the samples, which was where the animal was slaughtered. That might not necessarily be where that animal was from. So we have refocused our surveillance and I'll get into that here in a bit to show you how we have redone that.

These are just yearly totals. This is Fiscal Year 1990, this is Fiscal Year 2001. Don't know why this doesn't show up with a number, but you can see our surveillance has

increased here in 2001. We have looked at over 5,000 samples so far this year.

This just shows, actually the next one is better if you would to the next one. The proportion of the samples we obtained from downer animals versus just straight CNS symptom cases. And right here this is 2001. As you see approximately 4,800 is our total submissions to our National Veterinary Services Lab. This does not include any of the veterinary diagnostic labs that we are working with. And of that 4,800 samples, approximately, well 4,464 were obtained from downers or fallen stock. So we are really focusing on that proportion of the population.

This one, if you remember that map previously with all the numbers and all the states, we sat down with our field people that are familiar with animal movement patterns, with trading patterns, with where slaughter houses are routinely obtaining their animals, where they are drawing their population, especially where aged dairy cattle is from. And we divided the U.S. based on these movement patterns into these eight regions. So like the Northeast, most folks might be familiar, there's a few - plants that are located in Pennsylvania that are pouring animals primarily here from the Northeast.

So we divided this into these regions. We then took the population of that region and looked at that in

accordance with the OIE guidelines as a mini country. So we looked then at the OIE guidelines for that population for that region, took that number and then doubled it to give us our goal for surveillance.

So we set our goals based on that and we did meet all of these goals with the exception of this one in the Central Region. I think the next slide is, yes, shows the numbers. Now if you can go back, you notice I said we didn't meet the goal in the Central Region because nowhere is cattle population in the U.S., you will notice these states here in the middle of the U.S., there's a lot of cattle there but they are primarily beef cattle, they are not dairy cattle, and we didn't factor this in as we were laying out these regions. And beef cattle, that's really not the highest risk population where we would find BSE. The highest risk population is probably your aged dairy cattle that got fed a lot of concentrates. So we might need to readjust this region somehow.

We are continuing to try to increase our surveillance. As I said we are looking for highest risk population, downer cattle, aged cattle, more than two years of age, primarily dairy cattle. I would like to make it kind of, I think there has been various things said about, you know, Japan testing every animal. I think everybody has heard about in Europe all the increased number of testing

that they are doing. And the experience in Europe has shown that randomly testing healthy young animals at slaughter is really a waste of resources.

If you are going to find the disease, look for your highest risk population, which is going to be an adult animal with some type of clinical signs. Obviously now it doesn't have to be classical clinical signs of BSE, but an animal that is down for whatever reason, is sent for emergency slaughter, that died for an unknown reason, that's going to be where you are going to find the disease. So this is where we are trying to target our population or our surveillance at this point in time.

So as I said, we are increasing our surveillance in the downer cattle, we are making every effort to get every CNS condemned at slaughter. 3-D 40 plants, those of you who aren't familiar with this terminology, 3-D 40 means down, dead, dying, diseased, these plants, obviously not the dead and diseased animals wouldn't be going for human consumption, but some of these plants could be inspected for human consumption. Many of these are killing these animals and obtaining the product for pet food production, but this is a primary source for the highest risk animals and we are trying to work with these plants to get samples there also.

Renderers, we trying to work with renderers. If we can get some of these fallen stock foods of animals that

died for unknown reasons, we are trying to figure out a way to obtain more samples there, but we've run into a few challenges.

I think that is pretty much it on surveillance. Let me just run through these real quick. Actually if you go back one slide, we did import live cattle as I mentioned earlier. U.K. and Ireland, we imported 496 from - Ireland prior to 1989, actually about 330 of those were from the U.K. There are three of those animals remaining alive in the U.S., three lawn ornament cattle up in Vermont, overall very happy cows.

There was a brief window of time in 96, 97 where we imported some animals from continental Europe. These were primarily beef cattle from Germany, Austria and Italy. We have traced down all of those animals. The ones that we haven't yet obtained, they are under state quarantine. We are monitoring them and if the animals get sick, they die, the owner wants to get rid of them, we purchase them for diagnostic purposes. There are six of those animals remaining. Next one, this will be the last.

We did import some cattle from Japan. These were ragu cattle, the specialized beef cattle from Japan. I think we imported approximately 240 from the period of 93 until 99, at which point in time Japan got food and mouth disease and we stopped that. But these are the ones where

we have just started this process and some of these animals are imported primarily for genetic production, semen embryo collection. They have moved around quite a bit. So we are still tracking a few of them down. The ones that we know are still alive and located in these states.

There are about 66 of them so far that have already been slaughtered. We don't believe these animals really present a significant risk because the traditional production methods of the ragu cattle doesn't include any type of concentrate in their food. They are fed such things as grains. You hear all the rumors about saki and beer and various things, and silkworm cocoons, various kinds of protein.

So I think that's it for the relevant slides.

DR. BOLTON: Lisa, I have a question for you. How were the two cases of BSE picked up in Japan? Were they random surveillance or were they targeted?

DR. FERGUSON: They were not random surveillance. The one case, the first case was an animal exhibiting clinical signs, and they picked her up and actually on histology, at least based on the reports that we have had, and I have to admit sometimes it has been a challenge to get accurate information from the Japanese in regards to this case. I think we are sort of way down on their priority list at this point in time. But the first animal was

exhibiting some type of CNS clinical signs. Histology, it did have spongiform change. I don't know if it had any other lesions, but did have spongiform change. They ran a prionics test, which was negative, but then immuno was positive. They also sent that sample to the U.K. and the actual confirmation was done in the U.K.

DR. BOLTON: And was that somehow, did that directly lead to the second case? Was the second case picked up in the same herd, I forget.

DR. FERGUSON: I don't think it was. I'm not as familiar with the second case. But I know in response to the first one they have really increased their surveillance and testing. Actually, go ahead Dr. Crawford.

DR. CRAWFORD: On one of your slides you had the acronym I think for the veterinary diagnostic laboratory system.

DR. FERGUSON: Yes.

DR. CRAWFORD: But you didn't really discuss it. I think that is a safeguard that we very often overlook. You want to elaborate on that a little bit. I know you were on short time, but I think that is as important as any other factor you mentioned.

DR. FERGUSON: Yes that is, and I would be glad to go into a bit more detail on that and make two significant points.

DR. CRAWFORD: Not too much more detail.

DR. FERGUSON: Not a whole lot. The veterinary diagnostic labs, we've worked with a lot of the state university diagnostic labs. We have helped train some of their pathologists. And in those labs where we know they are using the same standard operating protocol as our National Veterinary Services Lab to look at the appropriate section of the brain and they are looking for the same thing we are, we will count those numbers in our surveillance, and that is a very useful tool.

But the second significant point along the same lines, with the diagnostic labs, also with all of the university teaching hospitals, there is a data base out there that kind of keeps track of CNS cases and maintains, sort of monitors does that level change, are there increased numbers of CNS reported, is there anything unusual going on. And I would think that if we had a significant problem with the BSE you would see an increase in those, and there has been none.

DR. BOLTON: Are those cases immediately referred to your labs for examination of prion disease or have they already been examined, they are not?

DR. FERGUSON: Right. Those numbers that are recorded on here is from a veterinary diagnostic lab. Primarily they have only been examined on a

histopathological basis at that diagnostic lab. Some of those will lend forward samples us to an immuno also, but primarily those have already been examined and they are not referred to us.

DR. BOLTON: Is it likely that in the near future either veterinary medical centers and/or state veterinary diagnostic labs or other labs would be asked or required to automatically send these, you know, brain samples from any CNS case to a central lab for confirmation? I mean this seems like sort of a good idea if one were really serious about surveying the country for the occurrence of the first BSE case.

DR. FERGUSON: Well it could be a suggestion. We are always looking at ways to increase our surveillance. We have certain constraints, especially fiscal and personnel constraints at our lab that we are trying to deal with. But also in that line, in many of these instances, for a neurological case, you know, a diagnostic lab will come up with a diagnosis, you know, listeria, whatever, some type of toxemia. Those types of things probably wouldn't necessarily need to be referred up, but it would just be those where you don't have another diagnosis.

DR. GAMBETTI: Two points. First of all I think I am glad to see that the number of tested animals is increasing, 5,000 has become certainly a better number than

the numbers that we heard before. Nevertheless it is still an extremely low number if you consider the number of animals that have been tested in Europe, that are in the one hundred thousand, and you correct this for the bovine population, cattle population of the United States, which is much, much bigger than the population in each individual European country. So I hope that these numbers will increase, because so far, in my opinion, I'm not very representative, I am encouraged by the fact that they did increase. But I hope that we'll hear a bigger number in the near future.

Now the second point I have is you mentioned an array of tests, the histology, immunohisto chemistry, so and then western blot. It was not clear to me, for example, those 5,000 samples examined to date in the year 2001, how many really have been examined by western blot, and rather than simply histology or immunohisto chemistry, and whether the immunohisto chemistry was done with autoclaving the section before doing, because that would enhance the sensitivity of the method considerably.

And before I stop I would say that in my experience, for example, about 20 percent of the cases of proven CJD, that we really see with autopsy are negative by immuno staining. So the immuno staining is definitely not as sensitive as the western blot. So having said that, yes

I would like to know how many of those 5,000 have been tested with western blot and what was the procedure.

DR. FERGUSON: I throw a huge caveat in here and say I am absolutely positively not a diagnostician or a laboratory person. Of those 5,000, very few of them have been run with western blot. Essentially all of them have been done with histo and immunohistic chemistry. On our RHC process I am not sure of the exact process. Beth might know.

DR. WILLIAMS: The technique that is used is hydro autoclaving formic acid treatment using the most sensitive techniques that we have available that work very well for BSE and the appropriate antibody. So I think it is appropriate testing and is good.

DR. FERGUSON: Can I actually go back a bit to Pierluigi's first point about increasing numbers, and I would just like to kind of throw a general caution out here as far as comparisons of numbers and comparisons of our numbers to comparisons in European numbers. If you remember some of the first slides that Bill showed, we slaughter you know what, 35 million steers and heifers in the U.S. a year. These are animals that are less than 18 months of age, and we slaughter what, how many adult animals, 7 million, 8 million, and that is the population that we are targeting.

So, you know, let's not think of a population of

100 million animals total as the population, let's think of the high risk population, the adults.

DR. JAMES: I would like to reinforce what Lisa just said, in that in 1999 I believe it was we slaughtered about 8 million cows and bulls, and in 2000 it was about 6 million cows and bulls. These are really the animals among which we have any reasonable likelihood of diagnosing BSE. So they are much smaller than the total national herd at large.

DR. BOLTON: Okay, now I want you guys to be honest. Who was first?

DR. BELAY: I was going to ask a question on the sensitivity of the western blot and the IHC or the immunohisto chemical methods. This could be a critical issue as we go into surveillance, especially for BSE, and I've been trying to clarify this issue for quite a while now. Dr. Gambetti said the western blot is definitely more sensitive than the immunohisto chemistry in at least human cases, and he has a lot of experience in this area.

But I was told that the opposite is true in animals, that the immunohisto chemistry was more sensitive than the western blot in, you know, testing for BSE or chronic western disease or other animal TSEs. I just wanted to clarify that issue. They are people with some experience in this area.

DR. BOLTON: Steve and Beth, do you want to respond to that?

DR. DE ARMOND: We find the western is very much more sensitive than immunohisto chemistry. Immunohisto chemistry, after formalin fixation, really knocks down the sensitivity of the system. So in our initial studies, gee back in 1987, 1988, we went to dissecting brain regions and doing western analysis and quantitative western analysis, and suddenly we shifted the pre-RP scrapie curves significantly over towards early, to finding early deposits. Our histo blot technique is essentially a western analysis with a tissue stuck onto nitrocellulose paper.

We find that it is as sensitive as western. We, in collaborative efforts with PR Luigi, we were unable to find PRP scrapie in one very peculiar case by hydrolytic autoclaving, and were very disappointed to find that he found that it was positive by western analysis, and after dissecting the brain into smaller pieces, we finally did find some positivity by hydrolytic autoclaving.

So definitely western analysis must be significantly more sensitive and the histo blot is comparable I believe to the western analysis, because it is done on frozen tissue that is treated exactly like a piece of protein. Histology, once it is formalin fixed, really loses it sensitivity for identification in the protein.

DR. BOLTON: There is however the caveat with western blotting and that is the sample that's taken can actually miss infected tissue, whereas with a slice of tissue you are covering a broader cross section of the brain.

DR. DE ARMOND: Certainly with an animal brain. The human brain we found the same thing. There are some forms of the disease, like the hyden hang variant, where if you don't get the temporal lobe and the occipital lobe, you miss the disease.

I want to say something else though with regard to testing. The comment was made that you shouldn't, it is a waste of money to test healthy animals, and yet from your experience the disease can be harbored in healthy animals. In fact it may not even appear in the lifetime of an animal but can be passed on to another animal. And the experience in Germany, as I understand it, a hundred cases of BSE have been identified in so-called healthy animals. So I think if we are going to be able to do what the consumers want, that is really verify and protect them from disease and tell them that this is a prion free piece of steak or brain or whatever they want to eat, we have to test even the healthy.

DR. BOLTON: Well yes, I'll sort of jump in and maybe not force Lisa to say this again. I think it is important to remember that even with healthy animals the

older animals are still, would be the population that you would test, and even in a healthy population. But still the unhealthy animals are still the most likely to be the sentinel case of a BSE infection. Okay, I'm overwhelmed. Ray you have had your hand up for awhile.

DR. ROOS: Lisa, I wondered how many high risk downer animals actually undergo surveillance. You mentioned that you are trying to obtain central nervous system material from animals that might never go to the slaughter house and get picked up by the renderer, or may just die on a pasture somewhere. What percent of downers do you actually think you obtain?

DR. FERGUSON: That's a good question, and I don't have an answer to that question right now. I don't know that we have an estimate of number of downers in the U.S. Bill, do you guys have anything?

DR. JAMES: No (laughter). Of course animals can go down at the farm and maybe never show up at the slaughter plant. So to my knowledge there is no good estimate at the number of animals that actually go down in the United States.

DR. ROOS: So I think, you know, it is a great idea to go after these high risk animals, but we don't have all that much of an answer as to how many there are and what percent we are really getting. And I think that, as you

said Lisa, efforts really have to be made to get that information and get those tissues, because they are the high risk animals.

DR. BOLTON: I see many hands again, and I fear that these are all about surveillance of some sort. Let me just put something out there for your consideration. At the risk of again beating this topic to death, I think we can conclude that surveillance is imperfect at this point, clearly. Surveillance needs to be increased as much as possible. But even that having been said, the surveillance of the cattle population, even the population that slaughter, will never be complete. So if we can accept those as factual conclusions, we then need to still go back and consider question one in the context of that imperfect surveillance, and I'll entertain questions that do not have to do with surveillance at this point. Bruce, are you sure this is not a surveillance question?

DR. EWENSTEIN: Well I'm not absolutely sure (laughter). I mean frankly what I was thinking is that yes I take your point about imperfect, but I wonder if it is possible, and it may have already been done or maybe could be done at a later time, to try to be a little more quantitative about that term, because we do have the numbers that are being surveyed, we do have the total numbers, we could make some guesstimates about the increased incidence

among the high risk population of cattle that you are targeting, we do have some guesstimates I suppose that could be put on the sensitivity of the current assays to miss a case, what the false negative rates would be with the tests that we are using.

And with all of that, would it be possible to provide, I mean not on the spot, but some number, you know, to the community that would say, you know, with current methodologies, there is less than an X percent probability that there is BSE in this country, because I think that really then, you know, allows us to put some sort of number on the rest of these questions, because the answer to whether you would want to eat brain or not depends on how secure you are with the system, in more than just a qualitative sense.

DR. BOLTON: Peter you were up before.

DR. LURIE: It is not a surveillance question, it is a surveillance statement and it in a sense goes to what Bruce is saying. Our group actually did a study which USDA perhaps does not agree with, but nonetheless we stand by it, in which we looked at the rates of cattle testing for older animals, just focusing on that part of our analysis, dairy cattle, looking at the NVSL data alone, for the period 1997 to 2000, and we did it for the states that had slaughtered the top 20 dairy cattle, took numbers of dairy cattle. And

we looked at again the fraction, the testing rate by state.

The variation between the top state and the bottom state among those 20 doing the most cattle was 600 fold. Now we'll hear I am sure in defense of this that animals move, and they certainly do. However, the testing is by the same state as where the slaughtering is because after all, that is where the samples are obtained from. And no matter how much animal movement there is in the country, it simply can't account for a 600 fold difference between states that are slaughtering a fairly large number of dairy cows. So we are very worried that beyond any question of the numbers of animals that are being slaughtered is the randomness, the number being tested, is the randomness, and I've brought along copies of our report for anybody who is interested.

DR. BOLTON: Well we are not going to hear that defended, because we're not going to take the time to go through the discussion. Dr. Crawford?

DR. CRAWFORD: Just about the imperfect surveillance. The other end of surveillance is what is the level of CJD in man, vCJD in man, and do we also believe that surveillance is imperfect or perfect, because I think if you are going to make one statement, you really need to address the other, and perhaps we haven't had adequate discussion or presentation with respect to that.

DR. BOLTON: Dr. Gambetti, would you like to make

a brief statement on that.

DR. GAMBETTI: Absolutely, the acid isn't perfect (laughter).

DR. BOLTON: Good, thank you. That was very brief, thank you. Dr. Piccardo?

DR. PICCARDO: I have a point of clarification and a question to Lisa, it is a clarification. My recollection is that there is compensation for the ranchers that say well here I have a cow that has a neurological disease. That - is or no, because that a lot will depend on that, how the surveillance is being done.

DR. FERGUSON: We don't pay direct compensation if they call us and say come out and investigate these animals. If disease was diagnosed we would pay compensation. But one significant point is if we go out and do the investigation, then we will take care of the carcass, and in many instances that is an incentive to them for us to take care of that carcass disposal.

DR. PICCARDO: But still, I mean, is if you don't go out actively and saying well we are going to give you money, would be incentive for the people to report it at least, I mean a lot will go unreported. No one would want to report any case, I mean it is a problem for them to come.

DR. FERGUSON: True.

DR. BOLTON: We want to take a break soon, and

we've had a tremendous amount of discussion now, which is sort of diffusing off of the subject, but revolving around the question number one, and I think it would be wise for us now to consider question one and perhaps take a vote if there is a votable issue. Again let me read the question. What is the public health risk to consumers that would warrant consideration of prohibiting the sale of bovine brain and products containing bovine brain for human use. And we are now reminded that those products could be beef bullion, could be dietary supplements, or brain itself.

So we are just going to focus on brain and products that would contain brain. And I had said earlier that the risks that I could think of were undiagnosed or pre-clinical BSE, either in cattle in this country or in other countries that are currently designated BSE free from which those products might be imported. If anyone has other ideas or ideas of what that risk would be, let's bring those out now. Otherwise I would like to get the committee's sense of whether or not they agree with that particular analysis of what the risk is. Bruce?

DR. EWENSTEIN: Well I think you've got the question right, but in order to answer this in a vote, it seems like you need to sort of have maybe a few levels, you know, very high, high, low or very low, I mean I'm not sure how the committee is going to vote on what is the risk.

DR. BROWN: Well we can't. If you change the question is there a public health risk, then you've got a votable question. And if you do that, you are going to have to vote on two questions. One, is there a public health risk concerning brain, and two, is there a public health risk concerning brain products. And that was emphasized by you at the very start. It seems fatuous I think to prevent someone from eating brain as a brain if he wants to, but it does not at all, is it all a question about risk that you know about and risk that you don't. And it is the products that really deserve attention.

DR. BOLTON: There is an alternate approach here, and that is to say that we do not have sufficient factual data to really vote on this question because of the lack of adequate surveillance data and other issues, but that these are clearly areas of concern that need to be addressed by the FDA in the future. It is sort of pushing the issue into the future without really dealing with it now. But I'm a little concerned that we would be voting on something for which we don't really have factual basis. Lisa?

DR. FERGUSON: I'd just like to put in I guess another plug, perhaps not, maybe a bit of a clarification on the Harvard assessment, and Bruce I think this might get into some of your suggestions about quantitating the risk or attempting to.

The Harvard assessment is not necessarily going to do, you know, a pinpoint quantitative risk estimate. It is more looking at pathways that BSE could have gotten into the U.S., pathways and implications for human health based on that. And also it will give us an idea of risk management measures and what might be most effective, what might not be most effective. It is a computer model. I think it will be a very good model.

I realize that it appears to have been delayed and I'll step up at least for our half of the department and say part of that has been we have been attempting to get them as much data as possible to make the model and the report as accurate as possible. Hopefully it will be out here very soon and I think it can be a very useful tool in the discussion, especially about this question.

DR. EWENSTEIN: Well obviously knowing the prior probabilities even in a model is critical to assessing the outcome of a test, because you know, the sensitivity of the test and the specificity of the test depends very much on, as you know, on the prior probability. So that is really very useful, you are right. But in terms of the Chair's question, I think it would be wrong for us to just punt this and say we don't have enough information. We've been asked in this, you know, virtual vacuum of knowledge, to make some very important decisions.

At this point I think the FDA and the community, as a large community, are asking us for our best judgment at this moment about the relative risk of these products that people are consuming right now, and it perfectly fine to put an asterisk at the end and say, you know, more data required, as we always do. But to just say we refuse to answer on the grounds that we don't have perfect data would probably mean we should never have these committee meetings.

DR. BOLTON: Then let's consider this. Let us consider, as Paul suggested, separating this into two questions, the first being is there a public health risk to consumers that would warrant consideration of prohibiting the sale of bovine brain, and secondly, is there a public health risk to consumers that would warrant the consideration of prohibiting the sale of products containing bovine brain for human use. Ray?

DR. ROOS: Are we talking now, today, or are we saying that there is a potential risk.

DR. BOLTON: Vote today, but that they would consider prohibiting. I guess they would begin considering. Would they ban or prohibit today, I don't think so. I mean the question is vague in its inception because it is asking about something that would warrant consideration, which certainly I would think this warrants consideration. Whether it warrants prohibition is something that has to be

concluded after the consideration.

DR. ROOS: Can we ask for clarification from FDA, because I get the feeling that we are going to get a question which is, you know, pretty obvious as far as the answer, unless maybe they could guide us.

DR. BOLTON: Dr. Brackett?

DR. BRACKETT: I think you've got it right. What we were looking at is is there enough evidence, enough scientific knowledge, and if so what is it, to not necessarily quantitatively tell what the risk is, but is there enough knowledge to warrant what direction we should consider.

DR. BOLTON: But are you asking us to launch a process of investigation and consideration, or are you asking us to tell you whether you should immediately begin to write regulations to prohibit. These are two different things.

DR. BRACKETT: Right. No we are not asking you if we should write regulations. We are asking you do you think that there is enough scientific evidence of a public health threat that we should begin looking at different alternatives such as that.

DR. BOLTON: Okay, so consideration is the proper term, and so I will go back to those questions. In fact, I think we can probably take a vote at this point.

DR. DE ARMOND: We are really talking about U.S. cattle or U.S. bovine, not anybody else. Is that, what does bovine mean here, U.S. alone?

DR. BOLTON: No, I believe this could be materials from BSE free countries that could be imported into the U.S. Is that right Dr. Brackett?

DR. BRACKETT: That is correct. A lot of these products may not necessarily just come from the U.S. They are in transit, trading partners.

DR. BOLTON: And again I'll state what I think was stated earlier, that the risk that I consider the greatest would be other countries that are currently BSE free but may in fact have significant BSE risk. Paul?

DR. BROWN: Like Japan. For example, vis a vis today and a month ago.

DR. BOLTON: Exactly. And perhaps other countries in the region. So the question first -

DR. LURIE: One exception to that I think is even the dietary supplements, there's little - to prevent the bovine brain from coming in from even the BSE affected country, right, I mean there's no regulation of the sourcing of bovine brain and so forth, right?

DR. BOLTON: No, I believe that is prohibited.

DR. BROWN: Oh yes, you can't import brain from a BSE country.

DR. FERGUSON: Right. USDA regulations prohibit that.

DR. LURIE: Well they may, but since the inspection rates are one percent a load at the border, you have basically no assurance of that, right?

DR. FERGUSON: Any product that comes in hits Agriculture first, and if it is an animal product it hits us first, and our inspectors, especially with all the animal health issues going on around the world over the past year or so, our inspectors are very keyed into anything that might remotely contain an animal product.

DR. LURIE: If it says so.

DR. FERGUSON: Yes, exactly.

DR. BOLTON: My point, we could also get into trans-shipment problems and that sort of area, but let's not dice this too finely. I have been asked to ask the public if there is anyone that would like to make a brief comment on this question before we vote, and we are going to vote soon on the question is there a public health risk to consumers that would warrant consideration of prohibiting the sale of bovine brain. Question one. Is there anyone in the audience that would like to comment?

Seeing none, I would like to vote on the question. Yes?

DR. STRONCEK: Just a quick question, just for

clarification. I thought I had heard that brain per se was not the purview of the FDA. Would you explain why we are voting on this?

DR. BOLTON: It is brain and products that may contain brain.

DR. STRONCEK: Yes, but you are separating it.

DR. BOLTON: Well I'm assuming that, is brain FDA regulated?

DR. BRACKETT: It could be if one wanted to use the Public Health Act. I mean if it was considered to be a threat to the public health. But more importantly, one finds it difficult to ban things that contain brain unless you know that they come from brain. So that's why brain was included.

DR. BOLTON: Okay. We are never going to get to this vote. Lisa?

DR. FERGUSON: Actually I just want to make sure that I understand the question, and we're asking is the risk there that would warrant consideration, correct?

DR. BOLTON: Yes. Consideration, not prohibition. In other words, should the FDA begin to consider this as an issue for prohibition, not necessarily concluding that they would prohibit. I think it is a fairly easy question. Should we take a voice vote. Yes. So Bill, would you like to call?

DR. FREAS: Yes. Going around the table, Dr. Roos?

DR. ROOS: Yes.

DR. FREAS: Dr. Ewenstein?

DR. EWENSTEIN: Yes.

DR. FREAS: Dr. Piccardo?

DR. PICCARDO: Yes.

DR. FREAS: Dr. Crawford?

DR. CRAWFORD: Yes.

DR. FREAS: Dr. Belay?

DR. BELAY: Yes.

DR. FREAS: Dr. Williams?

DR. WILLIAMS: Yes.

DR. FREAS: Dr. Nemo?

DR. NEMO: Yes.

DR. FREAS: Dr. Gambetti?

DR. GAMBETTI: Yes.

DR. FREAS: Dr. Blackwelder?

DR. BLACKWELDER: Yes.

DR. FREAS: Dr. Stroncek?

DR. STRONCEK: Yes.

DR. FREAS: Dr. Bolton?

DR. BOLTON: Yes.

DR. FREAS: Dr. Lurie?

DR. LURIE: Yes.

DR. FREAS: Dr. DeArmond?

DR. DE ARMOND: Yes.

DR. FREAS: Ms. Walker?

MS. WALKER: Yes.

DR. FREAS: Dr. Priola?

DR. PRIOLA: Yes.

DR. FREAS: Dr. Brown?

DR. BROWN: We are talking about brain, not brain product?

PARTICIPANT: Just brain this time.

DR. BROWN: Okay, a public health risk from brain, no. An individual risk from brain, yes, but that's not what we are talking about.

DR. FREAS: So that was a no vote on this question?

PARTICIPANT: That was a no vote, yes.

DR. FREAS: Dr. Cliver?

DR. CLIVER: Yes.

DR. FREAS: Dr. Ferguson?

DR. FERGUSON: Yes.

DR. FREAS: There were 18 voting, excuse me, our industry opinion on this question.

DR. PETTEWAY: Yes.

DR. FREAS: Okay, there were 18 voting people, industry had a non-voting opinion. There was one no vote,

Dr. Brown, and the rest all yes votes, no abstentions.

DR. BOLTON: That's correct. Now the second question, is there a public health risk to consumers that would warrant consideration of prohibiting the sale of products containing brain for human use. And we will have a voice vote on that as well.

DR. ROOS: Yes.

DR. EWENSTEIN: Yes.

DR. PICCARDO: Yes.

DR. CRAWFORD: Yes.

DR. BELAY: Yes.

DR. WILLIAMS: Yes.

DR. NEMO: Yes.

DR. GAMBETTI: Yes.

DR. BLACKWELDER: Yes.

DR. STRONCEK: Yes.

DR. BOLTON: Yes.

DR. LURIE: Yes.

DR. DE ARMOND: Yes.

MS. WALKER: Yes.

DR. PRIOLA: Yes.

DR. BROWN: Yes.

DR. CLIVER: Yes.

DR. FERGUSON: Yes.

DR. FREAS: Industry's opinion?

DR. PETTEWAY: Yes.

DR. FREAS: There were 18 yes votes, no no votes, no abstentions.

DR. BOLTON: Very good. So at this point it is 10:10. I would like to adjourn briefly for a 10 minute break and we will come back at that point and we will continue considering the other questions before we open it for a public hearing. Thank you. We will see you at 10:20 a.m.

(Break)

DR. BOLTON: I sense everyone is feeling relaxed due to the easy schedule today. But if we can take our seats, we'll resume the meeting. Before we proceed with the next question, Dr. Williams had a statement that she wanted to clarify with respect to the sensitivity of the western blotting test versus the immunohisto chemical test.

DR. WILLIAMS: Yes, what I just wanted to say to kind of clarify the issue for the committee and when we are looking at BSE and the comparisons that have been made between immunohisto chemistry and western blotting and some of the other diagnostic techniques on animals that are clinical, and this is a big study done by the European community, they were basically equivalent, so that certainly western blotting is not any better than immunohisto chemistry for the clinically affected animals.

And even when we look at sub-clinically affected animals, side by side comparisons, basically they are essentially the same as long as the appropriate area, anatomic area of the brain, is taken. So I don't people want to go away thinking that because the large cattle surveillance that is going on in this country is relying on immunohisto chemistry, that a lot of animals are being missed because they are not using western blot. That would be not appropriate.

DR. DE ARMOND: Where do you chose the brain section for immunohisto chemistry?

DR. WILLIAMS: At the obex region of the medulla and it is the area that is taken, and if that area is not taken and not representative for immunohisto chemistry, it is considered a no-test, and so the absolute area has to be corrupted in order to call it a test.

DR. GAMBETTI: But by not using the western blot, you limit yourself as you said to only the symptomatic animals, and so you really reduce the scope of your surveillance maybe not the way it is now, but in the way it should be in the future, that it is also asymptomatic animal that should be tested.

DR. WILLIAMS: Yes, and in fact immunohisto chemistry works very nicely in asymptomatic animals. Well it does in BSE and it does in chronic western disease and it

does in scrapie. Now exactly how far back you can go in the incubation period is going to vary to a degree. But it actually works very nicely and can pick up animals that are in the incubation period, halfway through the incubation period, at least by immunohisto chemistry. You might be able to get a little bit farther with western blotting perhaps, but that hasn't been, that has not been shown in natural disease as far as I am aware.

DR. BELAY: Just one comment. Testing healthy animals in my mind would only mix things if there is evidence of the existence of the disease. In the absence of any evidence of the existence of the disease, just testing healthy animals, there's no limit to it, and when would you say you have tested adequate number of animals to assure yourself that there's no evidence of the disease. So by concentrating on sick animals, downer cows and animals that are actually, have some evidence of a neurological disease, and sampling those animals, I think is a very good way of doing surveillance in the absence of any evidence of the existence of any disease.

DR. BOLTON: Again less we beat this point to death, I think it is clear that one needs to prioritize the animals that are tested. The clinically affected animals with some neurological disease would be top priority. Older animals would be second priority. All animals would be

lesser priority. So while we are not going to, I don't believe in this country, get to the point of testing every animal brain that comes to slaughter, if we prioritize in the manner just described, we are going to have the best opportunity, the most cost effective opportunity, to find the index case of BSE in this country and to insure the public that we are working in an appropriate way. Paul?

DR. BROWN: I'll reiterate that, and if we are going to do a survey of breast cancer we are not going to look at adolescent girls. It's as simple as that. This doesn't mean that if that is all they look at you will, you will always miss a case. But the prioritization which you just outlined is certainly the appropriate one. And the French, just to add one, two little postscripts, the French did a study to determine what it cost to make the diagnosis of BSE on a single cow. And if random testing was the method used in the cost per diagnosis, was a million dollars.

DR. DE ARMOND: For how many animals?

DR. BROWN: Every animal. That is to say, you know, that's the numerator, and it is every per diagnosed cow, per cow that turned out to have the disease, it cost a million dollars to make the diagnosis with random testing.

DR. BOLTON: Well I don't want, again, let's not beat this to death. I would rather go on to question two.

The next question we are going to entertain is the following. Is there a consistent and appreciable difference in infectivity of various sections or areas of bovine brain? And we had some discussion on this, I think that Paul, I correctly stated that yes there are differences, and Steve echoed this, there are differences in infectivity, but they are not apparently reproducible or predictable or useful in a regulatory manner.

So my personal opinion would be that the answer to that question is no, which then does not require entertaining the second part of the question, which is if so, what are the differences in relative degrees of infectivity in these areas. I would like to invite discussion on this question. Steve?

DR. DE ARMOND: Yes, I agree with that. So we know that the disease really focuses in the obex region in the brain stem, but does that mean you would then eat the frontal cortex freely. I certainly wouldn't, I wouldn't do it, and I certainly wouldn't eat the sacco region of the cord either.

DR. BROWN: Let's vote on this.

DR. DE ARMOND: I agree.

DR. BOLTON: Well first let me ask again. Additional discussion relevant to the point. Seeing none, we'll take a voice vote on that question.

DR. FREAS: Okay, I'd like to try to go backwards if I could, just to give Dr. Roos a little break. Going backwards, Dr. Ferguson?

DR. FERGUSON: No.

DR. CLIVER: No.

DR. BROWN: No.

DR. PRIOLA: No.

MS. WALKER: No.

DR. DE ARMOND: No.

DR. LURIE: No.

DR. BOLTON: No.

DR. STRONCEK: No.

DR. BLACKWELDER: No.

DR. GAMBETTI: No.

DR. NEMO: No.

DR. WILLIAMS: No.

DR. BELAY: No.

DR. CRAWFORD: (No answer)

DR. PICCARDO: No.

DR. EWENSTEIN: No.

DR. ROOS: No.

DR. FREAS: The industry position?

DR. PETTEWAY: No.

DR. FREAS: There were 17 voting members at the table. All of them voted no. There were no yes votes and

no abstains.

DR. BOLTON: Okay, the third question is, I think is based on the assumption that we are talking about BSE infected bovine neurological tissues, but I'll just read the question. Are there other bovine neurological tissues that, if used in consumer products, such as foods, dietary supplements, cosmetics and certain non-application drugs, could pose a significant health hazard. I'll open that up for discussion.

DR. BROWN: Is the question narrow, include spinal cord. I mean it doesn't have to, but we were talking brain, so I assume -

DR. BOLTON: Other neurological tissues than brain.

DR. BROWN: Spinal cord and/or peripheral nerve and/or para-spinal ganglia.

DR. BOLTON: Exactly.

DR. BROWN: Okay.

DR. BOLTON: Thoughts and comments?

DR. BROWN: Well I'll give you a thought. The answer is obviously yes (laughter).

DR. BOLTON: That's what I was looking for (laughter).

DR. BROWN: So we can probably vote on this right now too.

DR. BOLTON: Is there any other discussion? Okay, let's take a voice vote on this as well.

DR. FREAS: Mr. Chairman, what is essential is that we identify on the votes by name, and if you think it is unanimous, we can take a hand vote, show of hands, and then we'll identify the minority votes by voice.

DR. BOLTON: Okay. All those in favor of a yes vote on this question raise their hands.

DR. FREAS: One, two, three, four, five, six, seven, eight, nine, 10, 11, 12, 13, 14, 15, 16, 17 yes votes.

DR. BOLTON: All those opposed? I think there can be none. Any abstentions? No. So it is a unanimous vote.

DR. FREAS: I would like to state for the record, with the microphone on, that the industry position was a yes vote as well. So that means there were 17 yes votes, no no votes, and no abstentions.

DR. BOLTON: Now the second part of the question is if so, what are the differences in relative degrees of infectivity of these tissues. Since we haven't really identified specific tissues, and I don't know that we really have sufficient scientific data to discuss this or vote on it in detail, I would rather just pass on that and move on to the next question, which we may or may not be able to vote on either.

The fourth question is what physical, chemical, or biological factors of tissues and/or processes should FDA consider in reviewing procedures that may have the ability to reduce infectivity of bovine neurological tissues and products containing bovine neurological tissues. This is a very, very broad question and unfortunately we really haven't had any presentations this morning or yesterday that really address this issue. But again I'll open it up for discussion and we should try to keep within this area, not get too far afield on this discussion. Question?

DR. BROWN: I think that, I mean the simple answer is everything (laughter). No, really, every particular product that is processed has processing steps, most of which will have no effect on either removing or inactivating infectivity, but one or more may, and it has to be done on a product by product basis, and that is not facetious when I say all, you really do. Each product has to be evaluated with respect to all of its processes.

DR. BOLTON: Any other discussion? I don't think this really requires a vote then. The FDA will clearly hear that as a statement and we can move on.

Question five, what tests are available to ascertain changes in infectivity in products containing bovine neurological tissue?

DR. LURIE: Sorry, there is just one thing. Just

go back to four for one second. The other factor to consider is where the material goes. Paul's answer is really about the processing, which is of course right. But the other physical factor of the tissue is where it ends up, and if it gets, you know, implanted in the brain as in the case of dura matter, it strikes me that that would require particular attention.

DR. BOLTON: Well I think all covers that as well, so. I'm sure that they, FDA, has heard this. Dr. Brackett?

DR. BRACKETT: Right. I'll just elaborate a little bit on where we were going with that question. In the case of processing of foods for microbiological hazards, some things such as high fat may end up being protective of the organisms during processing, and so that's sort of the thing that we are looking at, either some tissues that may be protective of infectivity versus others.

DR. BOLTON: Well let me suggest this, that if the FDA really wants to consider that, some meeting in the future be devoted to that subject, because that is a huge, complicated, and difficult subject to deal with, and we are not going to get into that in any meaningful way in the time we have allotted today, especially since we have no experts here to present information.

So moving on again, what tests are available to ascertain changes in infectivity in products containing

bovine neurological tissues as a result of processing. To measure changes in infectivity we really have perhaps two or three types of tests. We have bioassays, the best of which are probably done in transgenic mice containing the bovine PRP gene, we have cell culture models that also can measure infectivity in a sense in looking at the production of new PRP scrapie, and I suppose we have in vitro conversion assays which are perhaps a step or two removed even from the cell culture assays.

But the true assays for measuring infectivity are in fact bioassays in living animals, and I'll invite discussion on that question at this point. Steve?

DR. DE ARMOND: Of course. I have to say though that prion protein, abnormal prion protein has correlated very well with that, and there are some of us who believe that the infective particle is the prion protein, although I know there are still some who don't. And so that, whether you want to call it a surrogate marker as you called it once before, the change in the amount the amount of protein we've shown and other labs have shown correlates well with infectivity. So if there was a process that decreased PRP scrapie, one would find a decrease in infectivity.

So there's the, let's put it into quotes, "surrogate marker" that correlates with infectivity, as well as the bioassays. Certainly they are probably still the

most sensitive of all the tests. I'm not sure about the tissue culture models. The two that, our two favorite, are the assays for PRP scrapie and bioassays in transgenic mice.

DR. BOLTON: Dean and then Bruce.

DR. CLIVER: I defer to Steve on what he just said. It happens that my lab is working on loss of infectivity by viruses like hepatitis A, and what accompanying physical changes we can identify, and I think this is important, the rub is though that at levels of safety that we are trying to impose on our food supply, we are looking at maybe five log reductions, and measuring PRP rays over the ranges that are available with present physical or chemical tests or immunological tests, I don't think you can measure five log reduction. So we are always in that dilemma that the tests are faster, they are certainly valid, but they don't have the sensitivity limits that we need for this kind of application.

DR. DE ARMOND: This so-called CDI, the conformational dependent immunoassay, will measure five logs and gets to the level of the bioassay. There is no question when you get down to that level there is an overlap with controls, so that once we get a sample at that level, we also go to the bioassay, to the transgenic mouse, to verify the presence or absence of the disease.

DR. EWENSTEIN: Actually I was going to speak to

the same point, and you know, I don't have a lab that does that kind of assay, but as I understand sort of the implication of the question, it is whether we have any tests available that would be able to tell us that a particular product that may have been made from high risk tissues, perhaps coming from abroad, was safe or not. And it seems to me from what I know, that we don't. But I think that sort of is the implication of the question as I see it, is there any way to track safety at this point in these products. I don't know if anyone else can speak to that.

DR. BOLTON: Well I suppose there is another word that is also implied in this question, and that is practical. Clearly transgenic mice could be used to bioassay, or in fact cattle could be used to bioassay samples of products that are imported, but they are not exactly practical tests in terms of surveillance or quality control issues. So again I don't think that this is a question we are going to be able to vote on, but I think our discussion will be useful to the FDA in guiding their thinking process for the future.

It should be clear to everybody on this committee that my thinking is that the abnormal prion protein is the infectious agent, so in saying that it is a surrogate marker for infectivity, it is somewhat of a technical statement, because when you are looking at PRP scrapie, you are not

looking directly at its ability to produce disease, as you would in an animal. But clearly in all cases where the association has been carefully examined, PRP scrapie is an exact marker, if you will, for infectivity, much like polio virus would be a marker for the ability to produce polio in animals or humans. So I want to be clear about that.

Additional discussion on other kinds of tests that either might be available now to detect either infectivity or perhaps PRP as a surrogate, or tests that people have heard about that are under development or should be developed in the near future. Dean?

DR. CLIVER: There are two issues here. One is here is an import commodity, can we test it, and I quite agree with Bruce, the answer to that is probably not only no today, but it will probably be no 10 years from now as far as adequate consumer protection is concerned. But I keep evoking this hazard analysis critical control points approach to food safety that has been in use since mandated by FSIS, their version, in meat and poultry slaughter processing.

What this question could be asking is do we have procedures, processing procedures, that could be put in place that would guarantee inactivation of TSE infectious agents and are there tests available to validate those processes, whereby if the processes continuously used and

continuously monitored, I'm not saying abroad, I'm saying right here in the United States, that a safe product would result. This is a very different thing from end product testing, and it is why our space program went entirely to this HACCP approach. They have no faith in end product testing for what goes to the astronauts.

So we could, if we had a test that we thought was valid, apply it to validating processes, and then just say if the process is uniformly employed, that's the route FDA has taken with seafood, with juices, and probably will gradually phase into other parts of food safety. So we need to be aware of that. But the Spock test grab sample, here it is at the border, that I don't think is going to happen.

DR. BOLTON: Good point. Paul?

DR. BROWN: Yes, I thought that the approach of using both an individual step clearance testing and an end product testing, the two of them being complementary, had already achieved consensus, not only by the FDA, but everybody else who is testing the safety of a given product. And there are critically wonderfully validated methods already using just western blot for the PRP protein to validate clearance. And clearly, just to give one example on the Bayer study in which western blot testing of the protein was beautifully correlated with infectivity, we know that this is a perfectly good, the best way to validate an

infectivity clearance number.

And the second part or the first part of Dean's question, what are the processes that will either remove or inactivate, that is a much tougher nut, because most of the things that we are dealing with have biological activity, and as far as we know, most of the two or three, the only two or three really guaranteed ways to knock down the tiger of infectivity destroy the biological activity. So that's the real problem, much more so than the actual testing of how much infectivity is removed.

DR. BOLTON: Of course the second problem is really that of the producer to solve, not of the FDA. I mean if you want to produce a product that maintains its activity, it is up to you to figure out how you can produce that and still keep it from being contaminated by prions or other infectious agents.

Additional discussion? Okay, I don't think we are going to vote on that. I don't think there is any point really. We've given appropriate discussion to the question. I guess I should ask, I realize that in sort of moving off of the agenda as published, we've taken up the questions without opening directly to public discussion, so I would like to invite any members of the public if they would like to step forward and give any thoughts on this particular issue.