U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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PUBLIC HEALTH SERVICE

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FOOD AND DRUG ADMINISTRATION

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TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES ADVISORY COMMITTEE

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MEETING

WEDNESDAY,
APRIL 15, 1998

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The meeting took place in Versailles Rooms I & II, Holiday Inn, 8120 Wisconsin Avenue, Bethesda, Maryland 20814 at 8:00 a.m., Paul W. Brown, MD, Chair, presiding.

PRESENT:

Paul W. Brown, MD, Chair
William Freas, PhD, Executive Secretary
Donald S. Burke, MD, Member
Linda A. Detwiler, DVM, Member
Leon Faitek, Member
Barbara W. Harrell, MPA, Member
David G. Hoel, PhD, Member
William D. Hueston, DVM, PhD, Member
Raymond P. Roos, MD, Member
Lawrence B. Schonberger, MD, Member
Eric Decker, PhD, Temporary Voting Member
Peter G. Lurie, MD, Temporary Voting Member
Doris Olander, DVM, Temporary Voting Member
Elizabeth Williams, PhD, Temporary Voting Member
Don Franco, DVM, Industry Liaison

SPEAKERS PRESENT:

Fred Bader, PhD
John Bailey, PhD
Raymond Bradley FRCVS, FRC Path
Stanley Gorak
Charles Green, PhD
Sharon Smith Holston
Mitch Kilanowski
Mike Langenhorst
Philip Merrell, PhD
Gerald Pflug, PhD
David Taylor, PhD
Dennis Walker

ALSO PRESENT:

David Asher, MD
Bob Brewer, DVM
Yuan-Yuan Chiu, PhD
Kiki Hellman, MD
John Honstead, DVM
Thierry Salmona

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P-R-o-C-E-E-D-I-N-G-S

8:07 a.m.

DR. FREAS: Mr. Chairman, invited Committee members, invited guests, members of the public, I would like to welcome you to today's meeting of the Transmissible Spongiform Encephalopathies Advisory Committee. I am Bill Freas . I'm the Acting Executive Secretary for today's session.

I asked the members of the audience if they have questions for anybody sitting at the table, please do not directly approach the members at the table. Please see me and I will relay your questions to the Committee members. So, we're asking you not to directly communicate with the table.

Today's presentations will be open to the public. The public is more than welcome to spend the entire day today.

At this time, I would like to go around the head table and introduce the members seated at the head table. 1'11 be starting on the right-hand side of the room. That's the audience's right-hand side of the room. At the first seat is our industry liaison representative for today, Dr. Don Franco

from the National Renderers Association.

If members would raise their hand just so the people in the audience can see who you are, I'd appreciate it.

Sitting next to Dr. Franco is Dr. Lawrence Schonberger, Assistant Director for Public Health, Division of Viral and Rickettsial Diseases, Center for Disease Control. In the next seat is Mr. Leon Faitek, consumer advocate on this Committee from San Diego, California. In the next seat is Dr. Raymond Roos, Chairman of the Department of Neurology, University of Chicago.

Next is Dr. William Hueston, Associate Dean, Virginia-Maryland Regional College of Veterinary Medicine. The empty seat right here in front of the podium will soon be filled by David Hoel, Professor and Chairman, Department of Biometry & Epidemiology, Medical University of South Carolina. Next, in front of me, is Dr. Linda Detwiler, Senior Staff Veterinarian, U.S. Department of Agriculture. Next is our Chairman, Dr. Paul Brown, Medican Director Laboratory of Central Nervous System Studies, National Institute of Neurological Disorders and Stroke. The next seat is mine.

Next to me is one of our new Committee members. I would like to welcome Dr. Donald Burke, Director, Center for Immunization Research, Johns Hopkins University to the Committee table. Next is Ms. Barbara Harrell, our consumer representative, Director, Division of Minority Health, State of Alabama Department of Public Health.

Next we have four temporary members for this session. They are Dr. Peter Grant Lurie, Visiting Assistant Research Scientist from the University of Michigan; Dr. Doris Olander, Research Associate, University of Wisconsin; Dr. Eric Decker, Associate Professor, University of Massachusetts; and Dr. Elizabeth Williams, Professor, Department of Veterinary Service, University of Wyoming. Welcome to everybody.

I would now like to read into the public record the conflict of interest statement required for this meeting.

"The following announcement is made part of the public record to preclude even the appearance of a conflict of interest at this meeting.

Pursuant to the authority granted under the Committee charter, the Director for the Center of Biologics Evaluation and Research has appointed

Drs. Peter Lurie, Doris Olander, and Elizabeth Williams as temporary voting members. In addition, the Director for the Center for Food Safety and Applied Nutrition has appointed Dr. Eric Decker as a temporary voting member, and Mr. Don Franco from the National Renderers Association as the industry liaison representative for today's meeting.

Based on the agenda made available, it has been determined that the agenda topics address matters of general applicability. Therefore, the general waivers previously approved by the Agency for all members of the TSE Advisory Committee including Drs. Donald Burke, Eric Decker, Elizabeth Williams are applicable for this meeting. Drs. Peter Lurie and Doris Olander have no financial interests to disclose.

Furthermore, it has been determined that all financial interests in firms regulated by the Food and Drug Administration which have been reported by participating members and speakers as of this date present no potential for an appearance of a conflict of interest at this meeting. The general nature of the matters to be discussed by the Committee will not have a unique and distinct effect on any member's personal or imputed financial

interests.

In regards to FDA invited speakers, the Agency has determined that the services of these participants are essential. There are reported interests which are being made public to allow participants to objectively evaluate any presentation and/or all comments made by speakers. These interests are as follows:

Dr. Raymond Bradley is a paid consultant to several firms both in the U.S. and abroad that may be affected by today's meeting. Dr. David Taylor is a paid consultant for Proctor & Gamble and Company on topics related to the Committee's activities. Dr. Robert Brewer had no financial interests to disclose.

In addition, the following participants were not screened for conflict of interest since they are here representing industry. They are Mr. Doug Anderson and Mr. Mitch Kilanowski from Darling International, Incorporated, Dr. Fred Bader from PhRMA, Mr. Stan Gorak from ICI Americas, Dr. Charles Green from Witco Corporation, Mr. Mike Langenhorst, ANAMAX Corporation, Dr. Phil Merrell, Mallinckrodt Chemical Company, Dr. Gerald Pflug, Soap & Detergent Association, Dr. Thierry Salmona and Mr. Reinhard

Schreiber from the Gelatin Manufacturers of Europe, and Mr. William Springer, the Coalition of Gelatin Capsule Manufacturers, and Mr. Dennis Walker of the Proctor & Gamble Company.

In the event that discussions involve specific products or specific firms for which FDA participants have a financial interest, participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the public record. A copy of the waivers are available upon written request to the Freedom of Information Office.

With respect to all other meeting participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firms upon whose products they may wish to comment upon.

So ends the reading of the conflict of interest.

Dr. Brown, I turn the microphone over to you.

CHAIRMAN BROWN: Thank you, Bill Freas.

Welcome, everyone. I think the FDA has stuffed into these two days, probably as full a plate as I can recall but we'll try and retain our

habitual light touch. The Committee which, happy to say, is a quick study is completely up-to-date on the background materials and can tell you the difference between palmitic, lauric and linolenic acids and the number of carbon items in each.

Therefore, I wonder if the speakers can exercise a certain amount of flexibility. You will be given your full allotted time, not a minute more. But it looks to me from the program as though there is the opportunity for an enormous amount of redundancy in subsequent speakers. Therefore, if you spot that kind of material having already been presented and which would be presented in your own presentation, I would beg you to skim over it rather quickly. We have an enormously full day, probably will not terminate until close to 6:00. Tomorrow looks like the same kind of day. Because of a certain amount of disgruntled response to the Committee's decisions about gelatin and dura meter, we're looking again, at least briefly at the end of tomorrow, at those two substances as well.

With that, we will begin our lengthy consideration of tallow. The first speaker is Sharon Smith Holston who is, and has been for many years, the Deputy Commissioner for External Affairs

for the FDA.

Sharon?

Yes, Leon?

MR. FAITEK: Dr. Brown, the issues here, that we will be talking about here are very similar to the gelatin. I'd like to go back to item 12 that was included in the packet. Perhaps it was my misunderstanding, but is the recommendations that are listed on page 2 of that item as described -- recommendations by the FDA, are those in keeping with the recommendations that this Committee made regarding the exclusion of gelatin products from BSE countries? If so, if they're not -- in the recommendations, is there any scientific evidence for that being?

CHAIRMAN BROWN: I think, Leon, we can defer that until the discussion of gelatin. Gelatin is really not going to come up until tomorrow afternoon. We're on tallow.

MR. FAITEK: I understand. But some of the issues are very similar between these two items.

CHAIRMAN BROWN: And do I understand you correctly to say "well, if the FDA is going to not introduce recommendations that are in total accord with the Committee, then maybe" -- well, I don't

know exactly where you're going with your thought.

MR. FAITEK: Well, somewhere along that line.

CHAIRMAN BROWN: Yes. We can only do what we're asked to do, Leon, which is provide advice. The FDA makes the policy. My reading of what the FDA did was that in broad terms and in many of the specifics, they followed our recommendations and our advice to them. I would expect no less from them with respect to tallow.

MS. HOLSTON: Well, can I at first at least correct the record and let you know that I am not here to start the discussion about tallow. I am here really just to welcome you and to thank you, frankly, on behalf of FDA, our lead Deputy Commissioner Michael Friedman and myself for being here and for the work that you're about to do to help advise the Agency on TSEs.

You've dealt with this subject obviously in the past. Many of you had helped us to develop some very important guidance documents on gelatin, on dura mater and safe sourcing and use of human plasma derivatives. Today's meeting from our perspective is just another very important step as we try to look at the safety of the products that we

are supposed to be regulating. We very much appreciate the help that you have committed to give us in, as Dr. Brown has said, a very, very full two days on some matters that are exceptionally challenging from a scientific perspective.

My own personal in-depth -- not in-depth, but certainly my own personal involvement with this issue goes back to last October when I lead a delegation of FDA staff to Europe to meet with European officials about the ban that they had proposed on specified risk materials that was passed last July. We wanted to meet with our colleagues in the European Union to emphasize to them, or at least to impress upon them, the impact of their SRM ban on the availability of critical pharmaceutical and other medical products in the United States, and the effect that that would have on the availability of these products as far as the American consumers were concerned.

In preparing for this mission, obviously, I was greatly impressed if not even a little bit depressed by the exceptional complexity of the issues that we were preparing to talk to the Europeans about. The fact that the scientific complexity was enormously compounded by the

political aspects, the social aspects of the issue, and yet, we were going over there to talk to them about a decision that they had passed. One of the things that surprised us when we got there and began to talk with our colleagues was how little awareness there actually was of the impact on the decision on the availability of certain medical products, not only for the American consumer but for the European population as well.

In our very first meeting with a high ranking senior official in DG3, he assumed, obviously, that we were there to promote US trade and that we were there on the behalf of the American pharmaceutical industry. It was necessary for us to take the time to explain to him that no, we were not a trade delegation. That we were, in fact, there in the interest of public health and to explain in some detail what the impact of this decision would be on their consumers as well as on ours. Needless to say, recently when they decided that the issue was so enormously complex that it was in everyone's best interest to put it off still further. It has now been postponed until next January while they continue to evaluate these issues. That was gratifying to us and many of us hope that in some

ways, our trip and the explanations that we made had at least some impact on causing them to take a pause and to give this issue some second thought.

In the meantime, of course, we continue to look at the issue. Coming up in June, the Joint Institute for food safety and applied nutrition which is a joint endeavor between FDA and the University of Maryland, will be holding a workshop on TSE risk in relation to source materials, processing and end product use. The workshop will consider what is known and what's critical to learn about the potential risk of TSE transmission in these kinds of products. I think the answers that you all are going to try to provide to us to the questions on today's agenda, will also go a long way to helping us deal with some of those issues. I hope that all of you will be able to attend the June workshop as well. The sponsors include among others, the Virginia-Maryland Regional College of Veterinary Medicine, and we have representatives from international, academic, manufacturing and governmental organizations.

So, you have an enormously full agenda and I don't want to take up any more of your time. I just did want to say that on behalf of the

Commissioner, the Acting Commissioner, Dr. Friedman and myself, and all of us in the Office of the Commissioner, we very, very much appreciate the effort and the commitment that you're putting into helping us with some very difficult and very complex issues. Thank you.

CHAIRMAN BROWN: Thank you, Ms. Holston.

The next item on the agenda is an open public hearing. I'd like to ask Bill Freas to proceed from here for a few minutes.

DR. FREAS: Dr. Brown, we had published an announcement of this meeting in the Federal Register, at that time asking anyone who was interested that we would afford them the opportunity this morning. I have not received any responses to the Federal Register notice.

Is there anyone in the audience at this time who would like to come and address the Committee.

I see no responses at this time. We will have two more open public hearings. If you would like to speak at one of those two open public hearings, please see me during the break or during lunch or after today's meeting. The other two open public hearings are scheduled on your agenda for

11:00 a.m. tomorrow morning and 3:45 p.m., tomorrow afternoon. So, if you'd like to speak at those, please see me.

Dr. Brown, I turn it over to you.

CHAIRMAN BROWN: Now we kick off the tallow seminar with Dr. John Bailey who is the Director of the Office of Cosmetics and Colors in the Center for Food Safety and Applied Nutrition. He will provide us our initial background information on the topic of the day, "Tallow and Tallow Derivatives."

DR. BAILEY: While we're setting up the overhead projector, I'd like to ask Dr. John Honstead to elaborate a little further on the June workshop concerning transmissible spongiform encephalopathies.

DR. HONSTEAD: Good morning. I'm John Honstead. I'm a veterinarian with the Center for Veterinary Medicine, NFDA.

I want to reiterate what Ms. Holston has already said. These announcements are out on the front table. This is going to be a very positive effort to accomplish relative to understanding TSE risks. This workshop is going to be held at the University of Maryland. It's going to consider what

is known and what is critical to learn about the risk of TSE transmissions and it's going to cover three primary areas: source materials, processing and the use of the end products.

The purpose is to define the state of current knowledge and to identify practical guiding principles for evaluating the risks posed by transmissible spongiform encephalopathies. There's a registration form on the back of this announcement. There is also guidance for sending in and presenting a poster. We have the speakers set, but there's still a lot of communication that can be done. The evening of the first day is going to be dedicated to viewing posters. The second page tells you how to get your poster submitted. It would be very useful to have a good assortment of posters.

So, we invite you to register for this meeting. It's June 8th and 9th, again, in College Park, Maryland at the University of Maryland. Thank you.

DR. BAILEY: Thank you, John.

Good morning. I would like to welcome the members of the Transmissible Spongiform Encephalopathy Advisory Committee, the speakers, the

audience, and to thank you for participating in this meeting of the Committee.

I would also like to thank the FDA Planning Group with Drs. Asher, Hellman, Chiu, Fang, and Honstead, and Ms. Vincent for their considerable efforts in organizing this meeting, and to Don Carrington and Lark Lambert of the Center for Food Safety and Applied Nutrition for their help. And of course, to Dr. Freas and also to Lynn Larsen who is the executive secretary for the Food Advisory Committee for their organizational and coordinating skills.

This meeting of the TSE Advisory Committee continues the Agency process of assuring the safety of FDA regulated products with regard to the risk to health posed by transmissible spongiform encephalopathies. This remains a challenging issue because of the continuing evolution of scientific knowledge about these agents. Last April, the Committee considered the safety of gelatin in FDA regulated products. The question then was "should FDA continue to exempt gelatin from restrictions imposed on other FDA regulated products in light of new information about inactivation of the TSE agent during manufacture?" In this meeting, we will focus

our attention on the safety of tallow and tallow derivatives which, like gelatin, is a processed ingredient.

What I would like to do is to provide, as introduction, a chronology of events and a little bit more background information so that you'll have this information as you hear the other presentations and deliberate on this issue.

Bovine spongiform encephalopathy is a transmissible, progressively degenerative neurological disease of cattle similar to scrapie in sheep. Other such diseases are Kuru, Creuzfeldt-Jakob disease in humans, scrapie in sheep and goats, chronic wasting disease in deer and elk and transmissible mink encephalopathy. These diseases, collectively known as transmissible spongiform encephalopathies are characterized by an incubation period of several years during which there is no visible indication of disease, a relatively short clinical course of neurological degeneration, and eventual 100 percent death. There is no known treatment or cure and there are only limited methods for determining whether or not a non-symptomatic animal is infected.

Since BSE was first diagnosed in Great

Britain, more than 170,000 cattle from approximately 33,000 herds have been diagnosed with the disease. BSE has been reported in native cattle in France, Switzerland, Portugal, Republic of Ireland, Northern Ireland, the Netherlands, Belgium and Luxembourg. Because of our concern about possible risk to health, FDA beginning in 1992 issued a number of letters to manufacturers of FDA regulated products requesting that bovine derived materials from cattle in countries designated by the USDA as countries where BSE exists not be used in the manufacture of FDA regulated products.

I'll summarize these briefly. In November of 1992, we sent a letter to manufacturers of dietary supplements expressing concern about the use of brain, nervous tissue and glandular ingredients in these products. In December of 1993, we sent a letter to the manufacturers of drugs, biologics and medical devices requesting that bovine derived material from BSE countries be avoided. This request excluded pharmaceutical grade gelatin.

In August of 1994, we sent a letter to manufacturers of FDA regulated products for animals requesting that bovine derived materials from BSE countries be avoided. In another letter sent at the

same time to manufacturers and importers of dietary supplements and cosmetics, the Agency recommended that products containing certain bovine tissues and extracts of other ingredients derived from these tissues not come from BSE countries. FDA excluded dairy products, gelatin and meat from this recommendation.

The same letter also explained that USDA had issued regulations to prohibit the importation into the United States of certain tissues and organs from ruminants from BSE countries to protect livestock in the US. The USDA regulations permit under conditions, the importation of collagen, collagen products, amniotic liquids or extracts, placental liquids or extracts, serum albumin and sera colostrum derived from ruminants from BSE countries for use in cosmetics. The USDA regulations do not apply to the imports of Finnish cosmetic products, bovine derived materials intended for human consumption as either Finnish dietary supplement products or as ingredients in dietary supplements or human food.

The next couple of issues had to do with evidence linking the new variant CJD and BSE. In March 1996, the British Government announced ten

cases of previously unrecognized form of CJD and speculated on a possible relationship to BSE. The Spongiform Encephalopathy Advisory Committee or SEAC in Europe postulated a link between the cases of new variant CJD and exposure to BSE infected beef, most likely before 1989. In April of 1996, WHO experts concluded that while there was no evidence of the link between BSE and the variant form of CJD, the evidence did suggest that exposure to BSE in the UK may be the most likely explanation. In October of 1996, investigators published data suggesting that the abnormal prion found in new variant CJDs resembles the BSE protein rather than that found in sporadic cases of CJD.

A more recent report last year from the United Kingdom concluded that new variant CJD is caused by the same strain of agent that has caused BSE feline spongiform encephalopathy and TSEs in exotic ruminants, transmitting the disease with a unique lesion profile in mice. This is considered strong evidence that the new variant CJD and BSE are linked. To date, new variant CJD has been identified in 24 people in Britain and France.

USDA regulations prohibit or restrict the importation of certain meat and other animal

products and by-products from ruminants that have been in regions in which BSE exists. Until recently, these regions included Belgium, France, Great Britain, Northern Ireland, Republic of Ireland, Luxembourg, the Netherlands, Oman, Portugal and Switzerland. On December 12, 1997, USDA extended the restriction on the importation of ruminants, meat and meat products from ruminants, and certain ruminant products and by-products to all of Europe. The USDA Federal Register publication noted that this action was taken because of import requirements, principally from the United Kingdom to other countries, less restrictive than those that would be acceptable for import into the United States, as well as concern about possible inadequate surveillance in Europe.

The USDA further noted that their decision was based on recent developments in Europe that suggested that the BSE agent may be present, but as yet undetected throughout Europe. Finally, the USDA noted that the risk posed by movement of products in Europe is increased in light of new scientific research that has identified BSE infectivity in bone marrow, dorsal root ganglion and trigeminal ganglion. The new research expands the

list of specific bovine tissues and organs of concern for BSE infectivity. The new rule does not prohibit the importation of semen, milk and milk products, hides and skins, tallow and tallow derivatives, and certain blood products used in microbiologic medium.

BSE has not been detected in cattle in the United States as reported from the surveillance and monitoring program at the USDA. The USDA, as of February 1998, has examined approximately 6,700 brains of US cattle exhibiting neurological signs, but has found no evidence of TSE. Since 1989, no cattle have been imported into the United States from BSE countries as designated by USDA.

I'd like to move on to the next slide. I'm going to go very quickly through some of the events that have taken place in Europe,t o provide a little bit of a perspective regarding the BSE and actions that are being taken in Europe. This is a difficult area to track and monitor. It's very complicated and sometimes it's hard to get information. So, this is my best effort at summarizing this for you.

The European Commission published a decision on the prohibition of the use of material

presenting risk of TSEs in July 1997. This prohibits the use of specified risk materials and prohibits the import into the EU of SRMs and requires certification. This directive was also interpreted to apply to process ingredients such as tallow and tallow derivatives.

The EU defined SRMs as skull, including the brain and eyes, tonsils and spinal cord of bovine animals aged over 12 months and ovine and caprine animals which are aged over 12 months. It also includes the spleens of any aged ovine and caprine animals. This particular action has been delayed and modified. The effective date now is January 1, 1999 with some modifications.

On March 5, 1998, the EC amended the cosmetic directive to specifically allow tallow derivatives in cosmetic products provided that the following methods have been used. They've specified the actual manufacturing conditions. For glycerol, fatty acids and esters, transesterification or hydrolysis at least 200 degrees C and 40 bar for 20 minutes. The second method which is for glycerol and soap was batch process at 95 degrees for three hours using 12 normal sodium hydroxide or continuous process of 140 degrees, two bars for eight minutes.

I believe a similar derogation has been established for pharmaceutical use of tallow derivatives, however, tallow itself is still subject to the SRM prohibition.

Most recently, the Scientific Steering Committee in EU has released its opinion on the safety of tallow derived from ruminant tissues. This was adopted at the SSC meeting held March 26th and 27th of last month. In this opinion, they defined tallow as fats obtained by pressing or any extraction system from ruminant tissues which are derived directly from discreet adipose tissue masses, fat extracted from skeleton muscles, mechanically removed meat, rendered animal waste including bones.

The SSC observed that the question is still open if tallow could transfer the BSE agent to animals or humans. Tallow can be considered safe after appropriate purification, but due to documented possible impurities, the raw materials should be obtained from appropriate sources. These sources being determined by geographical herd, animal and age criteria.

For countries considered to be BSE free or classified as a negligible risk, raw materials

fit for human consumption can be used to produce tallow without regard to minimal production process of removal of SRMs. For lower risk countries, SRMs should be excluded. The raw material should be fit for human consumption, and it should be subjected to a purification process. For high risk countries, SRMs should be excluded, the origin of raw materials certified, and the animals should be fit for human consumption, and the tallow should be purified. The SSC has not yet defined what constitutes a BSE free, low or high risk country. I believe this is their next task.

Finally, for tallow derivatives, the starting materials should be produced from raw material that is fit for human consumption and production processes use appropriate, validated and scientifically up-to-date methods for inactivating the agent. These processes, I believe, are to be defined by the respective scientific committees as they've done for cosmetics.

Okay, I'd like to move now on to some of the questions for the Committee and some of the background for those questions. The broad charge for the Committee today is to assess the safety of both imported and domestic tallow and tallow

derivatives used in FDA regulated products with regard to the risk posed by transmissible spongiform encephalopathies, specifically BSE. Tallow and tallow derivatives are subject to the guidance issued by the Agency for other bovine derived materials, namely, the materials that come from cattle born, raised, or slaughtered in countries where BSE is known to exist as described in regulations promulgated by the USDA; not to be used in the manufacture of FDA regulated products intended to be used by humans or animals.

FDA has not conducted a rigorous assessment of the manufacturing process for tallow and tallow derivatives and therefore, has not considered whether or not these ingredients can be subject to a different level of control than we currently have. One purpose of this meeting is to obtain information about the sourcing of raw materials, the range of manufacturing processes, and the dynamics of the market in order to better assess product safety and to consider adequate and appropriate controls for domestic and imported products.

Tallow is defined as "animal fat consisting primarily of the fully esterified fatty

acid, ester glycerol." Tallow derivatives are the products for the processing of tallow to break it into its component parts. The primary derivatives are, of course, glycerol and fatty acids. Other ingredients are obtained from the processing of tallow and these include various salts of the fatty acids, fatty acid alcohols, hydrogenated fatty acids, tallow glycerides which are principally partially hydrolyzed tallow and hydrogenated tallow and tallow glycerides. There are additional derivatives that are further down the manufacturing line.

When considering the manufacture of tallow, there are two basic categories, namely edible and inedible tallow. Each of these may be further processed into tallow derivatives. Representatives from industry will provide greater detail about this process. We've posted on the wall, both here and on the side wall down there, posters of these processes as we tried to put them together. These are sort of there for reference. We can mark them up or make changes as we go through if the industry has further comments.

The first process we're looking at is edible fat processing. This is the regulatory

responsibility of the USDA through the Food Safety Inspection Service and we will have our representative later from the USDA to describe this process in greater detail. Edible tallow begins in food grade slaughterhouses, slaughter establishments. The animals here are inspected and passed for human consumption. The edible fats are separated and then subjected to further treatment. On this chart, the edible fats are heated and cooked and then produce edible tallow. The refining, bleaching, deodorizing hydrogenation step goes underneath the edible tallow box which we've marked up here on these charts. The edible tallow can then be derivatized and either the edible tallow or the derivatives can be used in foods, drugs and cosmetics. These constitute different grades. Slaughter establishments with their own rendering plant are called captive renderers where the render will be right on site.

The inedible fat processing is regulated by the states and the Food and Drug Administration. In this case, a renderer takes materials not fit for human consumption -- and these can include dead animal slaughterhouse waste, restaurant waste and other sources -- and will obtain from these the

inedible fats. These are then heated or cooked to produce inedible tallow and again, the refining, bleaching, deodorizing hydrogenation stage should be, as shown on the charts here, moved down to after the inedible tallow step. Saponification produces soap, glycerol, fatty acid, fatty esters. Inedible tallow can be used in animal feed, cosmetics, industrial products and topical drugs. The saponified product can be derivatized and also used in industrial products, cosmetics and topical drugs. It's important to note here that you can not go from inedible tallow to edible tallow. Once it becomes edible tallow, it stays edible tallow. So, once it's in that category, it's my understanding that it doesn't go back.

For purposes of this discussion and from our own discussions on this matter, it is important to provide some definitions. Rendering is a process that heats raw material, raw animal by-products to release fat and remove moisture. You have two types of renderers: a captive renderer which is a slaughter establishment with rendering facilities. If this is inspected, then it can produce edible tallow or lard. Non-captive renderer is separate and is not associated with a slaughter facility, and

only inedible products can be produced. Animal feedstocks is a term used to denote the starting raw material used in the production and processing of tallow and tallow derivatives. This is sort of what goes in the front door. Cooking, heat treatment, that facilitates the release of fat.

Okay, I want to quickly go through the FDA regulated products starting with foods. For foods, tallow is animal fat is regulated as a food. Tallow is used primarily for cooking, principally in the frying of foods. Tallow derivatives consisting mostly of fatty acids and glycerin are widely used as additives in various types of food preparations. These ingredients must be obtained from food grade starting materials.

Tallow derivatives may be listed either as food additives for regulatory purposes or as GRAS substances. GRAS means "generally recognized as safe." A GRAS substance is not subject to pre-market approval as a food additive would be. Actually, GRAS is meant to cover food ingredients that have a long history of safe use. This was sort of a feature of the 1958 change in the Food, Drug and Cosmetic Act. GRAS substances include, for example, salt, sugar, baking powder, pepper and so

forth.

For dietary supplements, there's little definitive information concerning the use of tallow and tallow derivatives. For dietary supplements in oral dosage form, it's likely that they will use the same ingredients as drug or oral dosage forms. It is also likely that glycerin finds wide use in dietary supplements and that -- I think some dietary supplements are formed much the same way as foods would be. The substance is the actual supplementing agreement. That is the vitamin, mineral, herb or botanical rumina acid is not subject to pre-market approval by FDA. However, the excipient ingredients, the other ingredients that are in the product, are considered the same as food additives and must be either approved or generally recognized as safe.

For cosmetics, tallow and tallow derivatives, as you might expect, are used widely in cosmetic preparations. Of course, hydrolyzed tallow is soap. In addition, various fatty acid derivatives and glycerin are used in all types of cosmetic preparations, both in terms of rinse off products -- the soaps that you use and incur a short exposure time -- and also leave on products, the

creams and lotions and so forth. There's some material in your packet that talks about the different types of products.

The next overhead shows some of the long list of ingredients starting with tallow and some of the direct tallow derivatives as well as some of the more exotic, further reacted tallow derivatives. The numbers to the right are the count of products registered in our voluntary program, registration program. So, that count is out of about 16,000 or 17,000 products. That's how many products were reported voluntarily to use these various ingredients. Tallow has not been identified as a significant component of finished medical devices cleared for marketing based on information supplied in the manufacturing section of "Pre-Market Approval Applications for PMAs." It is not necessary for manufacturers to include manufacturing information in 510(k) submissions, although some may be provided.

Glycerin is present in a number of different types of medical devices. For example, glycerin may be used as a softening agent during the manufacturing process of collagen coated vascular grafts. Glycerol methacrylate is a monomer used in

the manufacture of some contact lenses. In this case, the monomer may be tallow derived or synthetic. Glycerol is also present in a number of wound dressings and in demineralized freeze dried bone preparations. Glycerol is likely to be contained in or have been in contact through, for example, tissue culture with many devices. The source of glycerine or glycerol, that is whether it's derived from animal or vegetable tallow or derived synthetically is not known in all cases.

Tallow is not identified as an ingredient in pharmaceuticals. However, tallow derivatives are used, including fatty acids, fatty acid esters, and salts, fatty alcohols, glycerides, fatty nitriles and amines and of course, glycerin. These ingredients are used in a variety of oral, topical, and ophthalmic products as well as rectal and vaginal creams and suppositories.

The next overhead gives a summary of the types of the products that a tallow derivative would be used in. Pretty much across the board in many different categories. The next overhead gives a little bit more detail. Dr. Chiu will be providing this in greater discussion later, so I won't go over this right now.

For biologics, tallow is not identified as being used in biologics. However, tween is used as a detergent in blood processing. Glycerine is used in blood products as a stabilizer.

For animal products, for veterinary drug products, the use of tallow and tallow derivatives is the same for human drugs, for veterinary cosmetics and shampoos. These are not regulated by FDA, however, it's likely that these products will use the same types of ingredients that you would find in human cosmetics and shampoos. Tallow is permitted as an ingredient in animal feed.

Again, the charge for the Committee is to assess the safety of both imported and domestic tallow and tallow derivatives used in FDA regulated products with regard to the risk posed by transmissible spongiform encephalopathies. In considering the charge, the basic questions are four. We have narrowed this down to four basic questions.

(1) "For tallow, does the available scientific information justify a change in the current FDA guidelines that feedstock for the manufacturing of tallow derivatives should not come from BSE countries as designated by USDA?"

(2) "If yes, should FDA consider changes to the guidelines for tallow used in foods and cosmetics?" This would relate to sourcing for countries, slaughtering procedures, how the material that goes into the tallow manufacturing process is selected and how this is processed in the rendering step.

(3) "For tallow derivatives, does the available scientific information justify a change in the current FDA guidelines that feedstock for the manufacture of tallow derivatives should not come from BSE countries as designated by USDA?" So, we've broken this down into tallow and tallow derivatives. This is two basic questions.

(4) "If yes, what changes should FDA make to the guidelines for tallow derivatives used in foods, cosmetics and drugs administered via various routes?" Again, on sourcing, slaughtering procedures and tallow quality controls. In this case, we're talking about edible versus inedible tallow, on manufacturing processes and process controls for the various tallow derivatives since these are produced in a variety of ways.

Since tallow and tallow derivatives are processed materials -- that is, manufactured using

several well defined steps, we would like the Committee to consider especially processing and process validation. What specific processing procedures are essential in assuming optimum inactivation of the BSE agent? What criteria should be considered in analysis or process validation data? Is there one manufacturing process that's superior for inactivating the BSE infectious agent? Conversely, are there manufacturing processes that should be avoided? In addressing these questions, it is important to consider the sources of raw material in manufacturing processes and the finished product type -- in other words, the exposure.

The agenda for today's meeting has been planned to provide a comprehensive overview of tallow and tallow derivatives, marketing and product use, manufacture and regulation to provide as much information as possible in considering these important questions. In addressing this charge, the Committee will be performing an invaluable service, contributing to a science based approach for decision making ont his issue to assure the continued safety of FDA regulated products.

Thank you.

(Applause.)

CHAIRMAN BROWN: Thank you very much, Dr. Bailey, for that background material.

I think I should have mentioned earlier, since in the absence of open public presentations this morning we'll be moving ahead, that we will follow Dr. Bailey's presentations and not take a break until the appropriate time. We'll go right on with Don Franco's presentation from the National Renderers Association and then continue on as though the break didn't exist until the break will actually come at 10:00. It is now shortly after 9:00 -- 9:01 to be exact.

Don, are you ready?

I have to say, I'm always delighted to see the origins of products that I would never have guessed would occur. I mean, from this presentation we just heard, we discover that when we use eye drops for contact lenses or cold cream or Flagyl, the material may have begun life as somebody's leftover T-bone steak in a restaurant. That's always amusing.

DR. FRANCO: We call it ingenuity, Paul.

I commend FDA for bringing together this public advisory committee to evaluate the regulatory aspects of the transmissible spongiform

encephalopathies. Again, I commend their concurrent requests of invitees to provide advice and recommendations as applicable to the Agency.

As a special liaison from the rendering industry, our representatives will heighten safety with relevance to tallow, both edible and inedible, with emphasis and their derivatives included in domestic and global issues that the Agency has an interest in assessing. The industrial presenters today are Mike Langenhorst, president of ANAMAX Corporation, Green Bay, Wisconsin, who will provide an overview of raw material sourcing, quality control procedures including hazard analysis, manufacturing processes, time, temperature controls, and product characterization and use.

Mike will be followed by Mitch Kilanowski, vice president of marketing, Darling International and president of American Fats and Oils Association, who will profile market dynamics with emphasis on production, imports/exports, and the applicable utilization of tallow highlighting foods, drugs and cosmetics. The group is accompanied by Tom Cook, executive director of our association who has assisted this initiative.

Tomorrow morning, condensed summary

comments of the industry's assessment of issues and regulatory responses will be profiled by Doug Anderson, senior vice president of Darling International.

Mr. Chairman, I want to assure you and the audience, we are committed organizationally to provide technical support on request. As associations go, we are relatively small, but we have a history of working with different branches of government for the past 65 years in the resolution of issues and we see no change in our directional mission. Thank you.

CHAIRMAN BROWN: Thank you, Don, for the introduction to the following three presentations: two by Mike Langenhorst and then one by Mitch Kilanowski.

Mike, you have the word.

MR. LANGENHORST: Good morning and thank you for the invitation to speak at this momentous occasion.

It was interesting coming in this morning, seeing all the familiar faces. They've gotten too familiar in the last couple of years, but as I said it's always interesting and enjoyable to be here.

As Don mentioned, my name is Mike Langenhorst. I'm the president of ANAMAX Corporation, a rendering company in Green Bay, Wisconsin. I'm also the vice president of the National Renderers Association and have served on the Industry Transmissible Spongiform Encephalopathy Committee for the last two years. So, the recap that you've seen this morning has included a lot of work from our industry.

I was asked to cover a few different areas. The agenda I'm going to be covering will be the history of the rendering industry. We're going to have a brief rendering school. Hopefully, it's not too simple, but it will try and get into a little bit more detail about the actual procurement of raw materials and processing, a little discussion on HACCP and a real quick summary.

Walking down the street, if you'd ask ten people what rendering is chances are maybe only one or two could actually tell you what rendering means. But all ten, as you heard this morning, use products that are part of the renderers' art whether it's soaps, tires, plastics, cosmetics, pet foods, glue or concrete, or even new synthetic lubricants.

The word "render" is actually an old

English verb that means to give back or to return, and that's exactly what the rendering industry does. It recycles by-products of the livestock industry by each year converting over 30 billion pounds of raw materials such as bones, fat, offal and carcasses of fallen animals for items that are used in our everyday life, up to eight billion pounds of tallow and six billion pounds of protein meals.

A sizeable percentage of the product is truly recycled. The tallow derived from animals or the fat of animals is fed right back to other animals as ingredients in animal feeds. The same is true of the protein which is fed to livestock and poultry as a portion of their growing rations. The balance of the tallow produced by US renderers becomes a vital and raw material for many hundreds of industrial or consumer uses as you saw earlier today.

It's hard to find the actual date in the first development of rendering, but there's a story about the Roman historian Pliny in 78 AD that describes the origin of soap. The story goes something like this. On Saple Hill near Rome on sacrificial and feast days, fatted calves and lambs are sacrificed as burnt offerings to Roman deities.

The melted tallow from the slaughtered animal mixed with the ashes from the burned woods and rains would pack this mixture together and run down the hill. Below the hill there was a small creek. Well, it was there that many of the women from town came out and did their laundry and found that the clothes got cleaner in this particular area. So, a thinking man immediately began to figure out ways, or to see what was going on in this area. They called this packed mixture with the dirt and the tallow and the ashes, saple. It's really from that term that saponification -- because Saple Hill was the area that it came from, so that's where the term saponification came from. So, it evolved to the point where they realized dirt didn't need to be a part of it, but soap started to be made from animal fats being mixed with the wood ashes.

Another part of the early development of the rendering industry was candle making. Starting with primitive tallow dips and rush lights, candle making became a widespread industry. The tallow candle came to an end roughly at about the 1850s and salt making became a growing industry on its own when a Frenchman by the name of Michel Chavreul demonstrated that fats were fat triglycerides. This

is what we had talked about a little bit earlier and I'm not going to get real hung up on the technical aspect. But the fact is, the finished tallow or fat is a triglyceride that when separated, produces glycerin and the different fatty acids.

Just a couple of the fatty acids and a little discussion when we talk about some of the quality characteristics it will be important. There are saturated and unsaturated fatty acids and the difference is whether there's double bonds involved in them or not. The species as well as the part of the animal that the fat comes from will determine the different makeup of the fatty acid composition.

The industry as we know it today came into being with the discovery that it was easier and more profitable to produce tallow and sell it to salt manufacturers rather than to have the salt manufacturer produce their own tallow and sell the soaps. The early history of rendering is not well documented, however, many cities had a local cheese maker, a brewery and a rendering company. It was really a family business. As you can see, transportation left a little bit to be desired at the time.

Open kettle rendering was a process used

in early days. Fat was put in a pot over an open fire where it melted. The tallow would rise to the top and was skimmed off. The remaining solids were air dried and sold as animal feeds. Technological advances in the rendering industry progressed to where batch cookers became a viable means of processing raw materials.

Along came World War II and along with it, many changes to the industry. The war effort created serious demands for tallow. Remember, tallow is a triglyceride or a molecule made up of glycerin attached to the fatty acids. It took ten tons of tallow to produce one ton of nitroglycerin. The war effort also increased the demand for stearic acid which was used for the manufacture of rubber and was a major lubricant used in drying metal for shell casings.

Synthetic detergents were invented to replace the use of tallow. So, after the war, other outlets were needed to be developed. In the 1960s, the first continuous rendering system, such as a Dupps Cooker and a Carver/Greenfield Evaporator Systems came into being. There were also improvements to efficiencies for batch cooking systems.

Since that time, there's been dramatic consolidation in the industry. In the 1960s, there were over 1,000 rendering plants in the United States and the majority were independent, not related to a packing house, and were primarily smaller family businesses with two to four batch cookers. There were a few larger companies at the time, but they were very small. You can see today, there are 292 plants that process over 30 billion pounds a year. Out of the 292 plants, approximately half of them are non-captive renderers, which means that they are not affiliated with a specific packing house, and the other half are packer renderers, or as was referred to earlier, captive renderers.

So, what we're going to do now is go from the history and really go into a little bit of the details of what rendering actually is, or a rendering school. When you fry bacon, you end up with three products: the liquid which is a tallow or grease, the solids which are the protein, and the moisture which is evaporated. In its simplest form, this is rendering. Animal by-products are cooked causing the moisture to be driven off and the fats separated from the animal tissue. So, it is with this analogy that we'll start our discussion on the

business of rendering.

To understand a little bit about rendering, I thought it would be best to talk about the quality of the finished products and then we'll digress from that to go through the process itself. But on the handouts that you have, I've identified different quality terms and we're going to go through these real quickly one-by-one.

Titre is a measurement of the hardness or softness of the fat and it's determined by recording the melting point. Under accepted US trading rules, titres at less than 40 degrees Centigrade are greases and those with titres above 40 degrees are tallows. The difference comes about from the different fatty acid composition. Tallows would come primarily from cattle or sheep material, and the greases would come from hog material or poultry material.

Iodine value is another measure of the hardness. It's really done by measuring the chemical and saturation of the fat and the results are expressed in the number of grams of iodine absorbed by a hundred gram of fat sample. So, it's just another method of measuring the hardness of the fat.

The raw color, or as it's referred to is FAC, the abbreviation for the Fat Analysis Committee -- it's a color standard that runs from one to 45 using odd numbers, with one being the lightest and 45 the darkest. A sample of fat after it's produced, or a sample of tallow is filtered and is compared with a color slide standard that's mounted on a circular aperture. What you do is you just compare the color of the sample to a different color that's in the slide itself. The refined and bleached color is used by certain people that we sell the tallow to. The soap industry and others have characteristics that they're looking for, what kind of color you get after it's refined and bleached. This analysis determines the Lovibond color after treatment with alkali and a specified bleaching earth. The Lovibond color is a much finer color, really, compared to the FAC color standards. It is product that has been processed under good conditions and usually very fresh material that have the lowest RMB colors.

Free fatty acids are pretty self explanatory. It's a measurement of the amount of the free fatty acid in the tallow.

MIU stands for moisture, impurities and

unsaponifiable matter. Moisture and fat arises from slight emulsification during processing. Impurities could be solids remaining in the tallow after rendering. The unsaps are any material in the tallow that will not saponify when mixed with an alkali. The MIU on tallows, the maximums you'll see is less than one percent and normally runs less than a half a percent with the impurities being probably .1 to .15 in most tallows.

Grade of filtration is another quality item that certain industries are concerned about. It's a method based on the volume of sample size that will filter in specified times under a certain temperature condition.

Peroxide value is a measurement that's used to determine rancidity. Rancidity is caused usually by oxidation. The method of assessing oxidation is by determining a peroxide value which is used primarily with edible oils and sometimes also with the use of fats or tallows in the feed industry.

Pesticide residue -- it's not really a quality characteristic, but it's definitely something that the rendering industry does. Use gas chromatographs to analyze tallows that are produced

for any concerns or any residues of pesticide that could be in it.

These are the AFOA specifications for different tallows and greases. You can see there's edible tallow with a titre at 41, FFA max at .75, and FAC color of three, and minimal if any MIU. You can see that there is no RMB listed, or the MIU is negligible. The independent, street renderer and the captive renderer that are now producing edible tallow are probably either producing an all-beef packer tallow, or a bleachable fancy tallow. Or depending on the source of raw materials, they could be down in the special tallow area. But I think for our purposes, we're going to talk about bleachable fancy tallow or packer tallow.

With a titre of 40½ to 42, maximum FFA on the packer tallow is two percent, unbleachable is four percent. FAC on the packer and bleachable is none. It's really more an RMB. Color is used so it's .5 or 1.5 for the bleachable, and a one percent maximum MIU. Choice white grease, which is hog grease, and could also be used in different products. Major difference is the titre, 36 versus 41. However, the rest of the specifications are very close to the bleachable fancy tallow.

Very briefly, just for your reference, I have included a couple of slides in the handout also that talks about animal protein. We don't just produce tallow and we don't just produce protein. When we go through the process, both products are produced. There are a few quality terms and then I also put together a little slide for reference that talks about different animal proteins that are available and then the characteristics of these different quality items in them.

Now, we're going to talk a little bit about procurement and raw materials and how that actually fits into what the renderer does. This slide highlights nine different types of raw materials. There are literally hundreds of raw materials that are processed by renderers in the United States, but in the interest of time we'll look at these just to get an idea of the concept of yields and different characteristics. The reason that the renderer is so concerned about yields is because this is really the backbone of our business.

To understand our business, you need to know how raw material values are calculated and the effect these values have on the operation. Now you'll notice that shop fat and caul fat -- they're

both fat products. They both have the same amount of units of protein in the finished meal, but there's a significant difference in the yield of the products. Shop fat would be the trimmings from a grocery store or a butcher shop and you'll end up maybe with a yield of 60 percent tallow and ten percent meal. Caul fat is taken from the stomach of the animal, has a much higher yield -- about 81 percent tallow and four percent meal. The difference between the 70 percent total yield and the 100 percent -- 30 percent is moisture that's in the product that's removed.

So, you can just see from these nine products, bones have about a 60 percent total yield -- only 15 percent tallow, 45 percent meal. The offal can be variable, maybe 14 percent tallow, 16 percent meal. Dead stock, ten and 22 and blood is negative tallow and 15 percent protein produced, so, only about a 13½ percent yield.

The calculation of raw material values, and this is what I talked about. To understand our business, this is a little bit of background. I won't spend much time, but just a little bit to give you an idea as to how we look at deciding values of raw materials.

We'll assume the tallow market is 16 cents a pound and meat and bone meal market is $180.00 a ton, or nine cents a pound. The fat that we saw, the yield was 60 percent tallow and ten percent protein times these values of 16 cents and $9.90 because there's 55 units of protein says that every 100 pounds of raw shop fat is worth $10.59. Assuming you have a handling cost for processing and transportation and administration of $5.00, that would allow you about $5.59 a hundred weight to pay for that product. There's about 70 pounds per head that's generated out of a normal animal.

Shop bones yield at 15 and 45 times their respective markets gives you a value of about $5.80, less the handling costs -- it's only about 80 cents a hundred weight value with about 150 pounds per head of material generated per animal. The offal, or the beef sets which are the heads, the feet and the stomach has a yield of about 14 and 16.6, so you can see that value is $3.73. If you have a cost of $5.00, there's a negative value to the offal. So, if you take the total evaluation of all of the three different items times their weights and values, you see that a carcass is probably worth somewhere in the area of $1.50 to $2.00 to the

renderer in its form of all these different products together. That depends on the different raw material sources, the different costs in doing it, but this is really the bottom line as to how we look at the values of products and values for payment.

Got a little bit of background here as to the makeup of raw materials. In general, all three of these next slides are going to show that packers and fabricators generate the large percentage of material and are processing more and more of it. Yesterday -- I think this represents about 1968 -- a 1,000 pound steer had about a 662 pound carcass. A lot of the carcass beef went to fabricators or grocery store chains where it was processed. Packer renderers processed about 36 percent of the raw material and independent renderers processed about 70 percent.

Today, you can see that steers have gotten heavier, about 1,114 pounds and there's very limited carcass beef that goes to grocery stores any more. Out of that, they generate about 714 pound carcass, but there's a trend towards leaner beef and total volume for the renderer is down. In 1978, there were 24 billion pounds of beef. In 1988, it's 23.4 billion pounds of beef and that trend is

continuing. So, there's a shift of about 3 to 6 billion pounds of raw material annually away from non-captive renderers. You can see the packer renderer has increased dramatically from 36 percent processed up to about 70 percent processed in 1988, and the independent is about 30. The trend is expected to continue where packer renders will probably be about 85 percent of the processing and independents will be about 15.

With pork, the same trends have started and are continuing. Not quite to the same extent because the packers were probably higher 20 years ago. But lean is still the key. There's less fat for the renderer and you can see that it has gone from 59 percent for packer renderers up to 64 with a projection at about 70 percent.

Poultry material: it's very evident that there's been a dramatic shift also. Same types of situations, plus the poultry processors have gotten much larger and are more fully integrated. The packer renderers which were only 25 percent in the past are roughly about 65 percent today will probably reach about 70 percent, where the independent will be 30 to 35 percent processing at that time.

On an input basis packers and fabricators generate about 52 percent of the raw material. Butcher shop chains and grocery stores generate about 22 percent. Miscellaneous products and dead stock are about six percent. Fast food restaurants are about 18 percent, and DAF and trap grease are about two percent.

There's another slide that I put in your handout that you can use for reference. It talks about trends in another way. But rather than take the time to go through that, that's just there for reference for you also.

Now we'll go on to the rendering process itself. No matter what type of system is being used, a simple description of the rendering process is raw material grinding, moisture removal and finished product separation. So, as we go through the different processes, in its simplicity, this is really what's being done by all the different systems.

I'm not an edible renderer so I'm not going to proclaim to be an expert. But I've got a little bit of background information and hopefully, I'll be able to answer any questions that you have. But an edible rendering system, as you can see, raw

materials -- and as they were identified this morning, are primarily products that are taken from edible processing plants. One comment I would like to make, it was mentioned this morning that only captive renderers have edible processing. That's not totally true. There are non-captive renderers also that procure material from inspected plants and have inspection at their facility to make sure that these raw materials are being handled properly. So, there could be captive or non-captive renderers that are in the edible business.

The raw material is ground and is put into an agitated tank that's heated to about 120 degrees. From this, the material goes through a disintegrator which is a grinder and goes through mechanical separation or centrifuging. The solid portion is a product that could be sold edible and as beef tissue. The liquid portion goes through another pump where steam is injected and the temperature at this point gets up to 220 or 225 degrees before the final separation and polishing of a vertical centrifuge. After that time, the fat is processed and is ready for sale as edible tallow. Edible tallow can be used either for edible or inedible. It can't go the other way. Inedible can

not be used for edible, but edible tallow can go either direction. That does happen from time-to-time.

Batch cooking is a process that's been used for inedible processing for quite a while. It begins with an accumulation of raw materials in a raw material receiving hopper. Normally, these come in large trucks. They're dumped into these pits which could hold anywhere from 40 to 120,000 pounds. They're commingled, so it's not just a specific raw material. Captive renderers have a raw material mix that's pretty consistent if it comes from a beef kill operation. There's a certain amount of bones and a certain amount of the offal and fat that's mixed together and it's pretty consistent. Independent renderers, however, more-or-less have available the products that are in their specific area and it could be a commingling of any of the hundreds of different types of raw materials that we talked about.

From the raw material receiving area, it is ground and is loaded into the cooker. The cooker itself is a cylindrical vessel approximately five foot in diameter and 12 foot long. There's a shaft that runs through the center and has paddles

connected to it that are used to agitate the raw materials inside. There's a jacketed shell around this cooker into which steam is injected. The heat transfer is accomplished when the raw material comes in contact with the jacketed cooker shell. As the cells burst, the moisture is removed through a condenser and the finished product -- which would be coming out is in a slurry at that point -- goes into a percolator drain pan. It's a slurry of tallow and protein together.

The protein portion, or the solids which are still somewhat greasy, go through a screw press where more of the finished tallow is extracted. The dry product, or the protein that's being processed is ground and screened and is sold as the meat and bone meal. The screwed pressed fat goes back and is mixed with the free fat that comes off the percolator into a tallow work tank. From there it goes through either centrifuge or a filter press, or both. It is then ready for sale as inedible tallow. Temperatures in the batch cooker range from about 240 to 270 degrees. Time of process, depending on raw materials, is usually two to three hours.

This is a schematic of two different processes. One is a continuous cooking system such

as a Dupps cooker or a stored cooker, as well as a restaurant grease operation and I'll go through each of these. The raw material, again, comes into the collecting hopper. It's ground and sized. The difference between this and a batch cooker is the fact that it is continuous. There is continuous material being put into the cooker and continuous finished product being brought out of the cooker.

Temperatures in the continuous cooker roughly range the same as the batch, probably 240 to 270 depending on which raw material is being used. The retention time is approximately 30 to 40 minutes. The same thing happens. As the product is cooked, the further it gets towards this end, the further processed the material is. The vapor is taken off, goes through a condenser, and the water goes to the waste water treatment system. The finished product comes out and goes through the drainer screen where the liquid tallow goes to the tallow processing and the solid portions go to the presses. The excess tallow is pressed out of the material, as well as some tallow off the drainer screen and they go for centrifuging and/or filtering or both, and go to the finished product storage where they're ready to be sold.

Restaurant grease is brought in either in bulk or in barrels and processed in different ways where it is cooked or heated. The finings from that product are settled out. The grease itself is also centrifuged and/or filtered, and the yellow grease goes to storage where it's ready for sale as primarily animal feed.

This is another type of a continuous cooking system. This is an evaporator system. It's a little more complicated to follow, but we'll try and get through it in a very quick means here. Raw material comes through a raw material pit. It goes through many different grinding processes. For the other two systems, it's ground to probably three-quarters of an inch to an inch. With this type of a system, you're grinding probably to an eighth or a half-of-an-inch. The reason for that is that you're pumping material through the whole system for processing. Once you get through the disintegrators or the small grind, the product is mixed at a ratio of about one percent raw material to five parts of finished tallow and are started to be pumped through the process.

These are falling film evaporators and each of the evaporators has many tubes in it that

are an inch-and-a-half to two inches in diameter. There's live steam injected on the second stage -- and when I'm talking about a lot of tubes, there could be 750 to 1,200 tubes in each of these different evaporator stages. The live steam is injected and heats the outside of these tubes. The raw material slurry is pumped through the center of these tubes, comes out and falls down into the vapor chamber. The finished product or slurry goes this direction and is pumped to the second stage. The waste heat from this first stage -- or from the second stage, I'm sorry, goes to the first stage and is used to pre-heat the raw material. Temperatures in the first stage are approximately 140 to 150 degrees, but this whole system -- you can see there's vapors that are being drawn to the condenser -- is under a vacuum. There's roughly 24 to 28 pounds or inches of pressure on this stage, so the boiling actually occurs in the first stage with the waste heat. The second stage has live steam on it, as I said, and is also under a vacuum. These temperatures in the second stage reach 240 to 270 degrees. Retention time in this system is about 20 to 25 minutes.

After enough moisture has been removed,

it is then pumped to the centrifuges or static screens for the separation of the solids and the liquids. The liquid portion goes to the work tank. The solid slurry still needs to have more fat pressed out of it. It goes to the presses. The extra fat that comes off, or tallow at that point, also goes to the work tank. The finished protein goes off for grinding and the tallow that's in the work tank is centrifuged and filtered and ready for sale.

There's one other process. It's a waste heat dewatering system and it's really a combination of the continuous cooker with an evaporator. The way that this system works is raw material is ground and subjected to a pre-heater at about 180 degrees. The material then goes through a twin screw press where a lot of the liquid is removed from the raw material. The press cake or the solid goes directly to the cooker, and the liquid goes to an evaporator that's using waste heat from the cooker to do some primary evaporation of moisture. The concentrated liquid is also then mixed with the press cake and goes to the cooker where it's processed.

Temperatures are the same as the continuous cooker, roughly 240 to 270, and retention

time in this system is about 20 minutes. But there's also some retention time of the tallow in the evaporator. This is also under a vacuum, so the temperatures in here are reaching over boiling, probably 220 to 230. After the material is processed, the free fat goes to the work tank and the slurry goes to the press. Again, where the fat goes to the work tank and the press cake is ground for meat and bone meal. The tallow that's produced here is centrifuged and filtered also and is then ready for sale on the open market.

So, in summary, we've seen the different processes, the different raw materials that make up the renderers' trade. This slide really shows the different finished products that are produced from the process. The dewatering, cooking and processing produce bleachable tallow. About 30½ percent of the raw material ends up as bleachable tallow. Special and choice white grease is about 2½ percent. Yellow grease and poultry fat is about 19 percent; meat and bone meal about 34½, brown grease one percent, blood meal one percent, feather meal 3½, poultry meal 4.7. Then hides are about three percent of the raw materials. They are not processed through the rendering process, but that's

one of the finished products that some renderers also handle.

The largest volume of product manufactured in a rendering process is waste water. It's about 52 percent of the raw material. So, only about 48 percent end up as the meal and the protein. That's usually about 20 percent tallow and 25 to 28 percent protein is an average production out of the total.

Next, I'd like to take a couple of minutes just to talk about the concept of HACCP as it applies to our industry.

CHAIRMAN BROWN: Mike, could I interpret you just a second? What happens to the waste water?

MR. LANGENHORST: The waste water?

CHAIRMAN BROWN: Yes.

MR. LANGENHORST: It depends on the process and the system. Many plants have primary treatment in the plant where there are one or two systems that the waste water would go through. There's a mechanical separation: dissolved air floatation systems or flocculants that are added and a large percentage of the product is recovered before the flocculants are added. They can be processed into lower grade tallows or greases. The

solids also could be recovered in the first stage at that point. After flocculation and processing, the waste water either goes to the municipal sewer treatment plant at that point.

Or a lot of us also have secondary treatment right at our facility, whether that be a biological system, aerobic or anaerobic. From there, it is sent to the local municipality. Or third, other facilities have waste water treatment lagoons and do a land spreading of that product. So, those are probably the three different options that happen.

Next, I'd like to take a few minutes to talk about the concept of HACCP as it applies to our industry. Although this magazine cover represents the implementation of HACCP for the meat industry, it could very well be on Render Magazine in the near future. About four years ago, Dr. Franco put together a guideline for the industry to use for the implementation of HACCP. In 1995 our company, as well as many others in our industry, went through the process of developing and implementing our own HACCP program. We are still not required to do this, but I would say roughly 70 to 80 renderers in the United States out of the 292, have already

started working under HACCP programs or implemented them. So, I think it's something that our industry is definitely aware of and is in favor of working.

I've taken a few excerpts from our HACCP program and I'd like to just outline these a little bit and give you a brief overview of the program that we did adopt ourselves. Traditional quality assurance programs at our company, as well as most renderers, were generally based on what management believed to be a good program. But at times it lacked uniformity as to what constitutes an effective program. Also, many of these programs were measurements of end product quality rather than proactive preventative systems of process control. HACCP introduces the principle of a preventative system of quality control. It outlines measures for extensive evaluations and control over raw materials, process, environment, personnel, storage, distribution, monitoring and traceability. So, it's really from start to finish that we're involved. The concept is simple, logical and a highly specialized system of controls to prevent the occurrence of hazardous or critical situations during the process of rendering.

Additionally, the HACCP program has --

inventory officials that we assume responsibility to develop a voluntary program to ensure regulatory compliance. To be effective, the HACCP program requires a commitment from our entire work force to work as a team to achieve the goals of planned prevention.

What I've done here is just outlined very briefly the critical control points that we identified in the rendering process. There are really three different areas. One is raw material, one of the critical control points. We have a multiple death policy, sheep or goat policy and CNS suspect cattle and foreign material. We do have letters and documents that go to all of our raw material suppliers. We go through our process and our qualifications with them. They all understand our requirements and sign sheets individually. We've also trained our drivers and our people in the plant to look for different things in the raw material.

The second critical control point is really the process itself. That's residence time and temperature. We monitor that daily, hourly, by the minute and make sure that we are abiding by the time and temperature requirements that we've set up.

On the meat and bone meal protein side, we have one critical control point and that's salmonella sampling program. The rendering industry, I believe 97 or 98 percent, belong to the API salmonella program. A very high percentage of compliance with that and that is a critical control point that the majority of the rendering industry is doing at this point in time.

On the tallow side, one critical control point is the pesticide check. As I said, that's not really a quality term that's used as a finished product quality of the tallow, however, it's very important that we check every batch or production for pesticides. If there would be any, it would show up in the fat and we would also be able to find it then in the other products that would be there. But before we ship any product, pesticides are checked.

Management must reassess TASA plans at least once a year or whenever one of the following occurs. Potential new hazards are identified. New ingredients could be added to your products. Processing steps or procedures are changed or new or different equipment are added to the manufacturing process. As I stated earlier, this is one of the

letters that we use with our raw material suppliers. You can see, the reason for this letter is to remind our suppliers of rendering raw materials, of our policy of accepting no sheep or goat material or CNS suspect animals from dead stock collectors or slaughtering operations. We have them read this letter and then they also have a sign-off sheet that you comply, as well as with the other areas of the raw materials.

So, in summary, we've covered a lot of information. The history of the rendering industry, we went through a little bit of a rendering school. And we've also discussed TASA. Our industry does provide many major services. We provide safe feed. We provide disease control. We contribute to the environmental health of our planet and we are definitely the original recycler.

Our industry, like many others, is always studying the past and looking to the future. In that light, I'd like to end with these three slides. Yesterday is but a dream and tomorrow is only a vision -- there's no bans, there's no BSE, HACCP is in place, there's no Asian crisis -- but today is a real bitch. So, on that note, I'd like to thank you for your time and your attention. If

there's any questions, I'd be happy to address them.

Thank you.

(Applause.)

CHAIRMAN BROWN: Thank you very much, Mike, for both an instructive and entertaining presentation.

It is now quarter to 10:00 and I think we can entertain, in fact, questions from the Committee members to Mike at this point.

Leon?

MR. FAITEK: Do you, as a matter of routine, exclude CNS materials from your raw materials?

MR. LANGENHORST: Yes. You saw that is our policy. We exclude CNS suspects as well as sheep and goats.

MR. FAITEK: All CNS material?

MR. LANGENHORST: Yes. CNS suspect, yes.

MR. FAITEK: How about unsuspected?

MR. LANGENHORST: Could you define what you're saying?

MR. FAITEK: Do you use any CNS materials in your raw materials at all, brain, heads, spinal cord?

MR. LANGENHORST: Oh, sure, sure.

MR. FAITEK: You do?

MR. LANGENHORST: Sure.

CHAIRMAN BROWN: Ray?

DR. ROOS: You mentioned that there were 220 or so renderers and it wasn't clear to me, in a way, who you're speaking for. And whether, you know, there may be a small renderer in one state or another or maybe many which, in fact, might use CNS material or have a purification system that's different from the one that you're speaking about here?

MR. LANGENHORST: I'm speaking on behalf of the National Renderers Association and API, probably representing the industry. The processes that I showed you are the processes that are used in our industry. There are no other processes that I'm aware of except maybe slight derivations from these generic slides that I showed. All renderers process -- you keep going back to the term "CNS."

There's no BSE in the United States and all renderers process all raw materials. The ban that was implemented this past year precluding the feeding of any of the ruminant material to ruminants or any of the mammalian material to ruminants has

eliminated or put up the so-called fire wall of any concern of cross contamination being fed back into the food chain. So, all renderers process the heads, spinal columns, or whatever materials there might be.

DR. ROOS: And all renderers are members of your group of Renderers Association, is that --

MR. LANGENHORST: Not all, not all.

DR. ROOS: No.

MR. LANGENHORST: No.

DR. ROOS: So, there may be someone who has practices different from what you're describing here? Is that --

MR. LANGENHORST: No, I wouldn't say that.

DR. ROOS: Paul, are we going to hear from European renderers as well? In other words --

MR. LANGENHORST: Are you getting at a specific question? Are you talking about the rendering systems in the EU -- in Europe versus the United States?

DR. ROOS: That was one of the questions I raised. I didn't know whether we were going to hear with respect to the European renderers, just in the sense that we're going to be talking about

tallow and safety of tallow and purification of tallow?

CHAIRMAN BROWN: Well, we have two speakers who probably know more than I would imagine on even the details of European, or at least United Kingdom rendering and they are Ray Bradley and David Taylor. Maybe we'll wait until we hear what they have to say and then if you still have questions, we can address them.

I have a couple of questions. For those who haven't done the arithmetic, 240 degrees Fahrenheit is the same as 115 degrees Centigrade and 270 degrees Fahrenheit is the same is 130 degrees Centigrade. Those of you who operate with titres are more interested in the Fahrenheit. Those of us who operate with titres are more interested in the Centigrade. Most of the work which has been done by us titre folks has been done at temperatures of about 121 or 132, 133, 134 and so forth. How much of a bother would it be to up the anti on the achieved temperatures in the rendering process from 240 to 270, say, to 270 to 300?

In other words, can you increment the operating temperature in the steam extractors, these cooking ovens, without undue sacrifice?

MR. LANGENHORST: There would be dramatic degradation to the finished product.

CHAIRMAN BROWN: I see.

MR. LANGENHORST: You would burn the tallow and the protein would be degraded.

CHAIRMAN BROWN: What's the maximum temperature that you can achieve and still have usable tallow?

MR. LANGENHORST: It depends on the raw material, and that's why I said there are ranges from 240 to 270.

CHAIRMAN BROWN: Yes, 270 would be about as high as you would want to go?

MR. LANGENHORST: Probably as high, yes.

CHAIRMAN BROWN: Is there any reason why the FDA hasn't included grease in this consideration, or is this understood when we're talking tallow we're also talking low titre grease? Is that right? Grease is up for grabs as well? Okay.

Other questions? Leon?

MR. FAITEK: What percentage of your product is imported? What percentage of your raw materials?

MR. LANGENHORST: Imported?

MR. FAITEK: From out of the country.

MR. LANGENHORST: There might be a little bit from Canada that the packing houses would use as raw material, but we're going to be talking about finished product importation in the next speaker.

MR. FAITEK: But all of your raw materials come from domestic sources?

MR. LANGENHORST: We collect them from domestic sources, yes.

CHAIRMAN BROWN: Yes, go ahead.

DR. HUESTON: Mike, can you clarify? You talked about this edible rendering system and just for my curiosity --

MR. LANGENHORST: Okay, well --

DR. HUESTON: -- so that crude fats coming into the surge tank and there's a disintegrator step, is there heat associated with either the surge tank or the disintegrator?

MR. LANGENHORST: There is heat in the first part. After the raw material is ground, it goes into the melt tank and that's at about 120 degrees Fahrenheit.

DR. HUESTON: 120 degrees Fahrenheit.

MR. LANGENHORST: So that it liquifies

the product to a degree and then it goes through the disintegrator where it's further ground for the separation step. The reason it stays at 120 or less is because the tissue that comes out is considered edible tissue. So, they don't want the temperature above the 120. The fat after it comes out past that point then goes through the other process of further steam injection and centrifuging. That's where the tallow itself is heated up to about 220 or 225.

DR. HUESTON: Great, thank you.

CHAIRMAN BROWN: We have --

Oh, yes, Barbara?

MS. HARRELL: I'd like to know how long has the process that you described been utilized? Number two, are these processes utilized to reduce infectivity or to ensure that you capture all of the tallow and that it is of high quality?

MR. LANGENHORST: First question was how long these processes have been used? Batch cooking has been around for 60 years probably.

MS. HARRELL: The entire process. The entire process that you talked about, the screening, the -- I mean, the entire process that you described, not just one part of it.

MR. LANGENHORST: There were different

cooking processes that came about at different times. The batch cooking process has been around roughly since 60 years ago. The centrifuging and filtering probably started 30 to 35 years ago. As I said in my discussion, the continuous processes started in the '60s also.

MS. HARRELL: So, this was not in response to BSE or anything, or TSE --

MR. LANGENHORST: No, this was not in response to the outbreak.

MS. HARRELL: Just trying to increase the capture of the tallow and the quality of it?

MR. LANGENHORST: Yes, improved quality and improved efficiencies.

Yes?

DR. LURIE: Could I just ask one follow-up question?

CHAIRMAN BROWN: Yes, sure.

DR. LURIE: Just to follow up on the question about the importation of raw material, you told us about sort of yesterday, today and tomorrow. Where do you see the future trend in this? Is there really enough raw material around for you to satisfy your needs, or do you anticipate in the future, the need for more importation of raw material?

MR. LANGENHORST: The question has to do with raw material sourcing. The total amount of raw material will decrease a little bit, but as population increases, people are going to continue to eat. What the trend shows is that the independent renderer produces less and there's less raw material for him, but there's more for the packer renderer.

What will happen is, there will be continued consolidation of the independent renderer and those numbers will decline in the future. You can only reach out roughly 150 to 200 miles for raw materials because of the concern of degradation to the raw materials. So, as far as importing raw material, that's not an option. You have to be located in proximity to where the materials are sourced in order to have a viable operation.

CHAIRMAN BROWN: Mike, you seem to be the right person to ask this. If you're not, maybe you could hoist it on somebody else. We read that the BSE epidemic probably, almost certainly, originated as a result of changed rendering processes in the United Kingdom that occurred around the late 1970s and involved, among others -- perhaps crucially -- the dropping from rendering plant

processes of a hydrocarbon solvent step.

Was that step ever used in rendering in this country? If so, was it stopped at about the same period?

MR. LANGENHORST: Hydrocarbon extraction was used back in the '40s and '50s. Maybe some plants into the early '60s, but has not been a part of our industry for probably 40 years. And while it was not a common practice in the industry, it was used by a few people to get a higher percentage of tallow out of the protein. It was stopped for a couple of reasons. One, it was a major safety concern. Then also, the advent of new pressing systems precluded the reason to continue using solvent extraction.

The hypothesis of change in rendering systems between the UK and the United States, there's a lot of different facets. It's not just difference of solvent extraction. Raw material composition was a major component of that. You look at the population of sheep versus cattle --

CHAIRMAN BROWN: No, no, we're aware of the different features.

MR. LANGENHORST: -- you know, you can go through all those different things.

CHAIRMAN BROWN: But the specific feature I asked about was the one you answered.

MR. LANGENHORST: Okay.

Yes?

DR. OLANDER: A question about headless animals. No headless animals are going into the system for inedible?

MR. LANGENHORST: That's our company's policy.

DR. OLANDER: Your company's policy.

MR. LANGENHORST: I don't know how the total industry is handling it. You can ask Mitch --

MR. KILANOWSKI: We've got the same policy.

MR. LANGENHORST: And a lot of the companies do. So, I don't want to represent the total industry on that, but a lot of companies are taking that approach.

CHAIRMAN BROWN: Ray?

DR. ROOS: I just wanted to make certain I understood these purification systems. You described a number of them with respect to inedible fat processing and you have 220 renderers. Is there one system that's primarily used at the moment or did they all kind of use different variations?

Maybe I'm wrong and -- my comments, getting back to the temperature issue here. If that's going to be an important one with respect to inactivation of the BSE agent, what does best with respect to temperature here? That is, the highest temperature for the longest time with respect to the purification scheme.

MR. LANGENHORST: The first answer would be that there is a combination of all of these different systems used. There's nothing that's predominant in the industry. They'll accomplish the same thing with different reasons for running different systems.

The second part of it is, we don't have BSE in the United States. And as far as anyone that's done work with that, I think Dr. Taylor is going to go through a lot of discussion as to where they found inactivation with different rendering processes.

DR. ROOS: My question was which one of these systems would have the highest temperatures for the longest time?

MR. LANGENHORST: Probably the batch cooking system.

CHAIRMAN BROWN: If there are no further

questions, we will take a break. It's exactly 10:00, and we will reconvene at 10:15.

Thank you.

(Whereupon, off the record at 9:55 a.m., until 10:14 a.m.)

CHAIRMAN BROWN: Would the various Committee members who are not seated please take their seats around the table so that we can begin the pre-prandial session?

What will happen now is that we will hear from Mitch Kilanowski, David Taylor, and Raymond Bradley. Because tallow and tallow derivatives have been presented to us as subsets of the topic, the appropriate breaking point would be after Dr. Bradley. That would bring us to an earlier lunch than was planned and I think I will plan on doing that. We will have the three stipulated presentations and then break for lunch which is likely to be closer to noon than to 1:00. We will then continue on a little ahead of schedule.

The only other point is that in view of our European representatives being, at the moment, on the sidelines after their presentations -- that is to say, the presentations of Drs. Taylor and Bradley -- we will invite them to take a seat around

the table to facilitate the discussion which may involve them heavily.

Now the presentation about market dynamics data from Mitch Kilanowski.

MR. KILANOWSKI: Thank you, Dr. Brown. Thanks for pronouncing my name right because usually it gets slaughtered more than the cattle that we're talking about.

First of all, happy tax day. I guess that's an oxymoron. Thank you for inviting us to make this presentation. My name is Mitch Kilanowski with Darling International, and I'm going to speak to you about edible and inedible tallow production in markets on behalf of the National Renderers Association. We do have some redundancy here, so I will not mention some things.

Edible tallow in the US production and uses. First of all, let me clarify something about edible tallow. Edible tallow when produced does not contain heads or spinal cords. That goes to the inedible part. Our production is approximately 1.45 billion pounds per year. Consumption and edible products, which is baking and frying fats, is approximately 350 million pounds per year. Consumption in edible products which would also be

other disappearance is approximately 800 million pounds. Much of that goes for soap, pet food and fatty acids. Exports of approximately 250 million pounds per year, but actually, I think that figure is much larger than that mainly because it gets exported out as tap white tallow mainly for soap manufacturing. Ending stocks are about 15 million pounds per year.

Edible tallow specification, as Mike went over, titre or titre -- whichever one we want to say -- is 41 degrees Celsius, minimum. Free fatty acid of 0.75 percent. FAC color which measures the color of the fat was a three max, which would be basically a pure white tallow. Moisture, 0.20 percent and impurities of 0.05 percent. Anything out of those specifications if shipped as edible tallow and it gets there and it's not in that specification, is rejected.

Tallow and grease production and uses in the United States: these figures are just somewhat of an average taken by the US Census Bureau. They don't change a lot from one year to the next. Production of inedible tallow, as you can see, is 3.5 billion pounds per year. Inedible grease is 2.8 billion pounds per year, for a total of 6.3 billion

pounds. The reason we take it together is because of the uses. It's not broken out into tallow and grease, so we have to sum them together.

Consumption in soap is about 250 million pounds per year. That has stayed somewhat steady I think mainly because they have been using a lot of edible tallow. Most of that is tallow and a small percentage of all hog choice white grease. Feed, our largest consumer is 2.2 billion pounds per year. A good portion of that is choice white grease. Lubricants, 85 million pounds per year and that would be for the rolling oil industry for steel manufacturing. Fatty acids, 625 million pounds per year. That has been steady for about the last four or five years also, mainly because they also are utilizing more edible tallow. Other products would be approximately 790 million pounds per year and some of that would also be pet food. Ending stocks are approximately 350 million pounds per year. Exports which are about two billion pounds per year contribute about a half-a-million dollars to this country's trade surplus.

The typical bleachable fancy tallow specification for sale to the fatty acid industry is as follows: titre of 40.5 degrees Celsius minimum;

free fatty acid of four percent max; FAC color of 19; refine and bleach, as Mike was saying, is another indication of the color of the fat. It's mostly a soap specification. Moisture is 0.50 percent, and an impurities of 0.25 percent. Anything out of those last two specifications is rejected if it gets there and it's above those levels.

I know everybody is concerned about the imports of edible and inedible tallow. These come from the Trade News Service which gets them from the US Census Bureau. As you can see, edible tallow imports -- this is metric tons. A metric ton is 2 million, 404.6 pounds per metric ton. As you can see, when compared to the total production in the United States, it's a very small percent that's coming into this country and it's all from Canada.

U.S. imports of inedible tallow in metric tons on a yearly basis. As you can see, Canada is the largest exporter of tallow into the United States. Once again, when compared to our total production, it's very small. I think a lot of these other smaller ones like Germany and Sweden -- I think it's material that's coming into the country that's probably just mis-marked as far as the tariff

considerations are concerned. New Zealand could be mutton tallow for the pet food industry also.

Exports of tallow and grease from the US. On that previous slide, we had Mexico on there just to show you we don't get anything in from Mexico. Our largest export market, I think at this time, is Mexico. We probably export, I think, 150,000 to 180,000 metric tons of tallow and grease to Mexico per year. The average figure there is about two billion pounds. Like I said, it represents about a half-a-billion dollars to this country's trade surplus.

As long as we continue to produce animals in this country and feed the world, we're going to have an excess in this country of tallow and grease, and we're going to continue to have exports of these levels. I would expect the 1998 figure to still be up there -- back up to around that two billion pound figure.

Insofar as prices are concerned, we are a cash commodity which makes our job just a little bit tougher. We fluctuate with supply and demand. These are our prices. We have about two or three different market sheets. One is the USDA, Jacobsen Publishing, and also the National Provisioner.

These are prices as taken from Jacobsen Publishing which are very close to the USDA sheet. As you can see, our prices do fluctuate quite a bit.

Bleachable fancy tallow prices move in pretty much a direct relationship with edible tallow since they are related. The next slide would be a monthly average. Prices at this time are around 14½ to 15 cents. So, you can see our prices do go up and down with supply and demand.

That's about all I have for my presentation. If anybody has any questions, I'd be happy to answer them.

CHAIRMAN BROWN: Does anyone on the Committee have a question? Yes?

DR. BURKE: I'm having difficulty going back and forth between metric tons and millions of pounds.

MR. KILANOWSKI: You take metric ton as 2 million, 204.6. So, if you've got 29,000 metric tons, you've got approximately 61, 62 million pounds.

DR. BURKE: Okay. Can you help me just in terms of the relative proportion of the total tallow which is domestically produced to the amount which is exported and the amount which is imported

with some common denominator?

MR. KILANOWSKI: Okay. You've got about 6.5 billion pounds produced in the US. Two billion pounds of that is exported.

CHAIRMAN BROWN: Again, so about a third?

MR. KILANOWSKI: About 30 percent.

CHAIRMAN BROWN: Twenty percent, about 30 percent is exported?

MR. KILANOWSKI: Yes, is exported.

CHAIRMAN BROWN: And what proportion of --

MR. KILANOWSKI: Now, that's total tallow -- 6.5 billion pounds is tallow and grease, choice white grease.

CHAIRMAN BROWN: Right. And about 30 percent of that total is exported?

MR. KILANOWSKI: Is exported, correct.

CHAIRMAN BROWN: In view of that -- and maybe this was your question, what is the purpose of any imports?

MR. KILANOWSKI: Well, it's coming in -- as you can see, the imports that were coming in are coming in from Canada.

CHAIRMAN BROWN: Yes, why?

MR. KILANOWSKI: Their markets are -- well, we also send tallow to Canada, part of NAFTA.

CHAIRMAN BROWN: Yes, so this is just a kind of a historical quirk and a market phenomenon where even though the total amount of tallow and grease that we produce is more than enough for ourselves, we still find ourselves importing for various reasons, a small amount from Canada and even less from other countries.

MR. KILANOWSKI: Right.

CHAIRMAN BROWN: Okay.

DR. BURKE: Again, can you put some number on that? I still haven't made the calculation myself. What percentage of the total tallow production in the United States is from imports?

MR. KILANOWSKI: I don't have a calculator with me, but approximately, I think, total imports are about 60 million pounds.

DR. BURKE: Sixty million out of 6.3 billion?

MR. KILANOWSKI: Yes, out of 6.5 billion pounds.

DR. BURKE: So, of the total tallow, we're talking about less than a half-a-percent or a

10th of a percent, roughly?

MR. KILANOWSKI: Right.

DR. OLANDER: One last question.

CHAIRMAN BROWN: Oh, I'm sorry. Yes, go ahead. Why don't you go ahead?

DR. OLANDER: Is there any trans-shipment through Canada from other countries?

MR. KILANOWSKI: Not that I know of because Canada also exports to other countries, also. Canada exports quite a bit to Korea, China, Germany -- where else? Quite a few different countries. The only reason it probably comes in here is because those markets like Southeast Asia has been hurt so bad. So, some of that has been coming into this country because our domestic usage over the past -- oh, since about May or June of '94, our domestic use has just been very good and exports have been on the decline here for the last two or three years. But that is going back up again.

DR. OLANDER: But you're not sure as to whether there is or isn't trans-shipment into Canada?

MR. KILANOWSKI: I'm not sure. I can't tell you that for sure.

DR. OLANDER: Okay, that's fine.

MR. KILANOWSKI: I doubt it though.

CHAIRMAN BROWN: Anybody in the audience know the answer to that question?

Ray?

DR. ROOS: On this overhead, it lists feed?

MR. KILANOWSKI: Yes.

DR. ROOS: So, that's animal feed in this country and what kind of animals?

MR. KILANOWSKI: Mostly poultry.

DR. ROOS: Cattle as well?

MR. KILANOWSKI: Poultry, cattle -- yes.

DR. ROOS: Okay. And that's still allowed? I thought there was some restriction on --

MR. KILANOWSKI: Just on the meat and bone meal.

DR. ROOS: Just on the meat and bone.

CHAIRMAN BROWN: What form is that? I mean, you don't obviously ladle out pure grease to an animal to eat, I would think. What kind of a product is that feed, I mean when tallow ends up as a feed?

MR. KILANOWSKI: It's an additive. It's an additive to the feed.

CHAIRMAN BROWN: Mixed in with

everything else, meat and bone meal and whatever else they're getting.

MR. KILANOWSKI: Right.

CHAIRMAN BROWN: Yes?

DR. BURKE: Can you say something again -- a little bit more. You said that maybe these really weren't from Germany or from Sweden?

MR. KILANOWSKI: Well, what I'm saying is that I think it's not really tallow that's imported into this country. It's probably some sort of a derivative but it comes in under a tallow tariff. Because I think it's kind of silly when you have imports of one ton.

CHAIRMAN BROWN: Thank you.

Now, we will move to the next speaker who is David Taylor. Who I guess, to the best of my knowledge, has performed the only published experiments on inactivation of the TSE agents that imitates or tries to duplicate, or is a scale-down process of rendering itself as opposed to a number of other kinds of inactivation studies which have not tried to duplicate rendering. So, David Taylor is from the Institute of Animal Health in the neuropathogenesis unit in Edinborough, Scotland.

Welcome, David.

DR. TAYLOR: Thank you very much, Paul. Thank you to the FDA for the invitation to come and speak to you.

Could somebody switch the projector on for me, please? Thank you.

Well, we see here the epidemic curve of BSE within the UK. We see that it was a down turn in 1993. This down turn was a direct cause of intervention in 1988 where there was a ban on feeding ruminants with ruminant derived protein. This was on the back of epidemiological studies carried out by John Wilesmith at the Central Veterinary Laboratory in England who, having surveyed a whole manner of potential risk factors, concluded that the only risk factor he could find for BSE was the feeding of meat and bone meal. So, we had the ruminant to ruminant feed ban introduced in 1988. The delayed effect is simply a reflection of the fact that the average incubation period for this disease is around five years.

Now, although we had the feed ban in 1988, we still have had a significant number of cases of BSE in animals born after that feed ban. In the case of those born in the period relatively soon after the feed ban, this was understandable

because the ban had not included any measures to seize and destroy food already in existence. On the other hand, there were a disturbing number of animals came down with BSE that were born some considerable time after the ban.

By May 1997, I don't know the count figures -- we had 106 SI and we had 32,000 odd cases born after the ban. As I said, many were born just after the ban. But what was discovered later was that the social infectivity for a number of these animals was cross contamination of ruminants by poultry and pig diets being manufactured in the same factories. Now, this should not have mattered because at that time, there was in place the specified bovine offal ban which should have removed all risky tissues and abattoirs. But what was discovered was that that regulation was not being very well policed at all. So, theoretically, BSE contaminated tissues could be getting into pig and poultry diet and then cross contaminating cattle feed.

Under the nice bit of information that John Wilesmith put together on this was that if you divide the UK up into different geographical locations and look over the period from the late

'80s into the '90s, you can see that in this region and in this region here, the incidence of BSE was actually accelerating. Whereas in most other areas, it was either relatively static or was, in fact, declining. It turns out that the north and the east are the areas within the UK where there's the most intensive pig and poultry farming. So, we've fairly good evidence that although the feed ban had a major effect and should have been more effective, there was some leakage into the system.

Now, in addition to John Wilesmith's theory about meat and bone meal, quite adequately confirmed by the down turn in the epidemic, it was decided around 1990 that we should conduct validation studies on the rendering systems used throughout the European Union. Surveys were carried out to determine what range of procedures were in existence, to define the time/temperature characteristics, to define particle size parameters, et cetera. A fairly major task, but after a fairly hefty effort by a large number of people meeting in Brussels on many occasions, we found that the processes could be defined, as you see, under these genetic headings. From traditional batch systems to the newer continuous systems which operated either

in atmospheric pressure or under vacuum, systems called wet rendering cooking either in the natural fat content or adding pre-heated tallow at the beginning of the process, and batch pressure systems.

I should say that of these batch pressure systems, the only one that was actually being operated in Europe was this one here. The other two were included as fall-back options in case everything else should fail. And so, using actual rendering equipment, albeit pilot scale equipment but genuine rendering equipment, we spiked large volumes of abattoir waste, in one case, with BSE infectivity, and in another series of experiments with scrapie infectivity.

I won't go into all the fine detail of the different processes. I would just comment at this stage, as a follow-up to comments made earlier on, that my understanding is that the range of techniques used throughout Europe are not that dissimilar to those practiced in the United States. Indeed, the equipment used to carry out these types of processes in many cases, again I understand, were probably imported from the United States. This does not, of course, mean to say that the equipment would

be used in identical fashion, but I think that is likely. Somebody may wish to comment on this later.

So, we carried out these experiments. The experiments were actually done, apart from this one, in pairs where we, on the basis of the genetic grippings for these processes, we defined minimum and average conditions, minimum average -- the exception the batch on the steam under pressure system. In the case of the BSE spiked experiments, when we studied the meat and bone meal output samples by assay in mice, with the BSE spiked material we found infectivity in four of these samples. Now, the BSE run was the first one to be done. As a mentor measure, when these results were submitted to Brussels, they put in place an interim decision which was to first of all, outlaw this system here. Because when we did titration of the infectivity titres, we found that there was, in fact, very little inactivation of infectivity at all in these meat and bone meal samples. And they redefined some of the time/temperature conditions applying to the other processes.

When we completed the scrapie spiked studies, we found that, in fact, all of the output meat and bone meal samples were positive except for

those produced by these systems using steam under pressure. Now, I should say that this is not evidence that scrapie infectivity is more thermostable than BSE infectivity because I would draw your attention to the fact that the amount of infectivity per gram of spike material that we managed to get in in the BSE run was just less than two logs per gram. Whereas, in the scrapie run, we might see it over three logs. So, the loads were different. One is not entitled to conclude, make any comments about thermostability between BSE and scrapie on the basis of this.

We did look at a limited number of tallow samples which I'll just mention briefly. The reason that the number of tallow samples was limited was because John Wilesmith, again in his 1988 paper, had already concluded that the nature and use of tallow in cattle feed did not equate with its known distribution, its commercial distribution in the UK. So, he, in 1988, he had looked at and excluded the possibility that feeding tallow was linked to the BSE problem.

As a result of the scrapie data, the EU issued this decision which, in essence, said as from April steer, countries within the EU that were

manufacturing meat and bone meal for use in any animal diets -- and be reminded, there had already been a ruminant protein ban placed in Europe since 1994. But people manufacturing meat and bone meal for inclusion into other species would thereafter have to use the process that I described here as the under 33 degrees process using steam under pressure for 20 minutes.

Just one anecdotal little bit of information that came from the rendering experiments. In one study where we ran the process at 72 degrees Centigrade -- and I should say that this is not normal rendering. I don't need to explain the background,b ut we did run one process at 72 degrees Centigrade under vacuum. With scrapie, we lost 2.3 logs of infectivity. Now, traditional studies in the past using these temperatures at the atmospheric pressure would suggest that the loss of infectivity within this temperature range is actually much less than that. In contrast, when we used the same equipment at atmospheric pressure and allowed the temperature to rise to 120-ish degrees Centigrade, the infectivity titre was reduced by a significantly smaller amount.

I would just say that this data actually

fit in with a number of other bits and pieces that we're collecting now, suggesting that things which aggressively and rapidly heat fix the disease specific form of the PRP protein, are likely to protect that from inactivation by heat processes and this in fact would -- this being under vacuum in a boiling of water here at temperatures below 100 degrees Centigrade. So, that's just an anecdotal side issue here.

Now, although the studies suggested at the 133 degrees Centigrade steam sterilization process was effective, the reasons for saying that in every day rendering, that might not be the case in worst case conditions. The reason I say this is that within the experimental rendering studies, we made every attempt to make sure that the brain material that we were adding to the bone and offal, et cetera, was thoroughly mixed in with that material. The reason being that we, of course, at subsequent stages wanted to take sub-samples and test for the level of infectivity. Of course, if it had been just distributed unevenly throughout the batch, these measurements wouldn't have meant much.

These red dots speculate on the distribution on the infected bits of tissue with the

large dark pieces of raw material in experimental rendering. I would venture to suggest to you that in every day rendering, as an infected brain enters the crushing and then the rendering process, that infectivity in that brain or the brain tissue, by the end of that process, is not going to be distributed in that fashion throughout the raw materials, but will be much more like this. In that case, if that is the case, one has to worry about the fact that the scrapie certainly -- for example, Bill Hadlow's study showed that over a complete scrapie infected brain, the infectivity titre could be 10^6 logs, and in some discreet parts of brain, you could get levels of infectivity up to 10^8 logs per gram.

The fact that I'm suggesting that infectivity is distributed like this in real life as opposed to this, to my mind is also borne out by the fact that the field evidence would suggest that meat and bone meal was not homogeneously infected, but you had clumps of infectivity, explaining why we have quite a number of herds with only one, two, or three cases. This would all fit with this idea of non-homogeneity. There's also data already in the literature which shows survival infectivity and ten

percent being homogenates infected with scrapie after 132 degrees Centigrade, steam under pressure for an hour from Maurizio Pocchaiari and also from Ernst & Race here at the Rocky Mountain lab. And I have data showing survival after 132 for an hour, or 134 for an hour with undiluted brain tissue.

Now, on to another aspect of rendering which was mentioned earlier on. Unlike the United States, the UK did use for quite considerable time, solvent extraction as an adjunct to rendering. In other words, already rendered material was then exposed to solvent extraction process, both to enhance the yield of tallow and to produce, at one stage, a low fat meat and bone meal which attracted premium prices.

What was observed was that during the late '70s and into the early '80s, the percentage of meat and bone meal produced using solvent extraction in the UK had declined pretty rapidly. It was thought that perhaps this had some association with BSE emerging in the mid-1980s, bearing in mind the five year average incubation period. The hypothesis was that since solvent extraction involves exposure to hot solvent, then dry heat and moist heat to drive off the residual solvent -- these processes

added to the rendering process that had already gone on beforehand may have collectively provided sufficient inactivation of these agents to at least keep them below the levels that would represent a meaningful challenge for cattle. Within the context of the rendering study that is -- we had only a rather limited capacity to do so with extraction studies out there in the field. But on the one occasion when we did, we saw an extraction as putting greaves through hot solvents. You drain off the fat laden solvent and then the solids are treated with dry heat and usually wet heat, and then pulverized to produce meat and bone meal.

In the one instance where we were able to do field studies in the natural solvent extraction plant, although the input level of scrapie infectivity here was rather low, the same level was detected, surprisingly, after exposure to hot heptane and then exposing the solid materials to dry heat at 100 degrees Centigrade and steam at 100 degrees Centigrade. However, recognizing that we were going to only have the limited capacity to look at solvent extraction in an actual commercial plant, we designed some simple lab studies to try and tell us a bit more about solvent extraction.

We knew from discussions with the renderers that these are the sorts of solvents that had been used in the UK. The last two surviving solvent plants in the UK used hexane and heptane respectively. It is those shown in yellow which we actually tested. The methodology was really high tech as you can see, test tubes -- we used bits of infected mouse spleen. This was mouse spleen infected with either the 22 A strain of scrapie agent, or the 301 V strain of BSE agent, added appropriate volume of solvent, heated to the appropriate temperature, and then followed up with the draining of the solvent and heating the solid materials with dry heat and wet heat.

Now, we recognized that one criticism that might be made of this study is that it in no way mimicking commercial solvent extraction because during commercial solvent extraction, it would be customary to percolate solvent through the raw materials, drain this off, distill it, to remove the tallow, and then recirculate that solvent. So, if infectivity was being removed in the tallow in the commercial process, we wouldn't be mimicking this here. However, two comments.

One is that the fat content of spleen is

way below the three percent level of fat that would customarily be in the meat and bone meal produced by solvent extraction. Furthermore, as I said, although limited, we did do some studies on tallow and the rendering experiments. Protocol I in both the BSE and the scrapie run happens to represent the protocols which were the least inactivating. In this case, in the BSE run, we got almost as much infectivity in meat and bone meal as we could in the beginning. And yet, under these conditions, we found nothing in the tallow.

Similarly, in the scrapie run, this was one of the most inactivating procedures as far as finding infectivity in meat and bone meal was concerned, but we found nothing in tallow. So, I would venture to suggest that these rather simple test tube studies are probably still relevant in drawing some conclusion about solvent extraction.

I'll finish just with letting you see the results of these studies which have just been completed. We have a starting titre here for both the mouse precise scrapie agent and mouse -- BSE agent. In all cases, there is some deduction if you look at the starting titre compared to the finishing titre after hot solvent -- in this case, heptane --

dry heat followed by wet heat. However, throughout the next three and final slides, you'll see that there are some trends.

Although it's probably not statistically significant here, the titre after exposure, even if the hot saline is actually slightly lower than after exposure to hot solvent and probably significantly so here. There are also suggestions here that the dry heat and wet heat process would combine with solvent at actually slightly less inactivating than the dry heat the processes -- now this would be compatible, in fact, with what I was hinting at earlier on. That procedures such as solvent extraction which can have a fixing effect on protein can protect the modified form of the scrapie agent from the damaging effects of heat.

I think in the next slide, you'll see that the same trend continues whether we're using hexane -- yes, heptane similar trends. Again, very little difference here. Again, that's a greater reduction than that. Again, the big pictures, the difference between here and here, certainly not very impressive. Same trends with the petroleum treatment. And again, these trends that I'm talking about here persist and the same for

perchlorethylene.

So, collectively, the simple bottom line from these data is that the amount of inactivation achieved generally by a complete solvent extraction process seems to be on the order of one log. That would be insufficient to explain, per se, the role of the abandonment of solvent extraction as the big trigger for BSE. But of course, if, as seems much more likely, BSE and its origins was multi-factorial -- and we've already touched on some possible factors today -- then this may, of course, have contributed.

There have been suggestions that "oh, it's big changes in the UK rendering process that triggers BSE." Well, there have been big changes in the UK rendering industry like the introduction of the new continuous systems, but I'm reliably informed that that occurred much more commonly during the early to mid-'70s. So, that doesn't fit with being the villain of the piece which triggered the whole thing. But in terms of conspiring as an additional factor, if you add that to what I just said about solvent extraction, what we know about increasing sheep populations, et cetera, et cetera in the UK, then I think the probability that BSE --

the precipitation of the disease was multi-factorial is more likely than not.

Thank you very much.

(Applause.)

CHAIRMAN BROWN: Thank you, David.

Now we'll hear from another representative from the United Kingdom, Dr. Raymond Bradley, who has been for a good part of his career -- perhaps all of it -- associated with the Central Veterinary Laboratory in the Ministry of Agriculture, Fisheries & Food, and has been a major player in the analysis and critique of BSE in the United Kingdom.

Ray?

DR. BRADLEY: Good morning, ladies and gentlemen. It's a pleasure to be here. I would like particularly to thank the FDA for the invitation. I always enjoy coming to the United States, my second visit in the last two weeks.

Like my busy life, there's a lot to say in a short time. The title of the talk is an update on BSE, the epidemic status controls, and tissue distribution of infectivity. I will deal with the controls last because it's more logical to have the update and the tissue distribution knowledge before

we deal with how we control the disease in the UK and in Europe.

I can skip quite quickly over some of my slides, and some I've already taken out because the points have already been covered. This is a simple graph of the epidemic which started windtop and came down, hopefully, to hit the bottom line. But this is an uncertainty at the present time. The point of prediction when it will hit that bottom line is somewhere in the region 2001 at the current rate.

I want to draw attention to specific points. Firstly, the total number of confirmed cases is over 170,000. The early stage at which the feed ban preventing the feeding of ruminant protein to ruminant animals was put in -- the delay, as David Taylor mentioned, of the down turn, as a result of this ban is due to the average incubation period of five years -- looked at more scientifically on the epidemic curve which represents all the confirmed cases of BSE.

It's important to look at some of the milestones. The first, histopathological confirmation in November 1986. The feed ban in July 1988, the SBO ban for animals in September 1990, but it had been previously put in to protect public

health one year previously. After the announcement of the ten cases of new variant CJD, there was no mammalian meat and bone marrow fed to any species of food animal, horses or fish in the UK. Absolutely none. So, the previous use of this for other species was eliminated at that point. In order to get the export of our materials including meats and live animals agreed with the European Commission, we undertook to clean out all feed mills which had meat and bone marrow or feed containing it, to clean and sterilize them. This was done by the first of August 1996, which was the date after which any cattle born would be unexpected to be exposed to meat and bone marrow feed, or to BSE even by feed.

But BSE isn't just a UK problem. It's actually a European problem. On this map which shows no reference to sizes of the epidemic -- I'll deal with that in a moment -- we see that in Western Europe, we have cases in indigenous animals, the ones in red and in pink. In some countries we have cases in imported animals from the UK, presumptively in the incubating stage of BSE whilst they were completely still healthy and could not be identified.

The full range of countries which have

reported cases of BSE is here. Those in red are those which have had cases in indigenous native born animals. Those in green, which have only had cases imported from the UK. Such cases do not present a risk providing they are identified, completely destroyed so they can enter no food and feed chain, and for practical purposes, can be discounted. That includes, actually, the Sultanate of Oman. The majority of the cases being reported, including all of those in Netherlands, Belgium and Luxembourg in the ones being reported currently, each one was born after their feed bans, their respective feed bans were in place. So, this cross contamination that David mentioned earlier is a feature in all countries.

It's just interesting to note that these feed bans down on this left side, and the dates upon which they were introduced in the different countries. For the most part, they were put in outside of Great Britain and Northern Ireland in 1990 in the countries which have had BSE. So that, it was two years later. The reason for that was that no other country developed a case until 1990. So, you can see that even the Netherlands and Denmark and so on, they had their bans in position.

The European Union didn't respond completely until 1994 when all countries in the Union had to adopt this ban.

In regard to the offals, a similar situation existed but much fewer countries adopted offals bans. Switzerland was the other important one behind the UK and I'll show you the importance of that in just one moment. Just interesting in passing in this rather old slide that in Iceland, they had a sheep offals ban from scrapie affected areas to all species in 1978. So, this was not something new to us.

If we look at the much smaller epidemics in the other countries outside of the UK, we can see, looking first of all at Switzerland, that the shape of the graph is very similar to the one I showed you first of all. It is rising and then declining in response to the feed ban, and presumptively also, in part, due to the offals ban. None of the other countries put in offals bans until much later on. In fact, quite recently in some cases. You see their epidemics, instead of declining, despite the ban has been in existence since 1990, they're actually on the rise. At this moment, we don't know whether they're close to the

top or they're going to be coming down as it has in the UK.

I want now to pass on to the cattle tissues in which infectivity has been found by bioassay. I'm talking now about field cases of BSE. This is not experimental. These are actual field cases of BSE. Infectivity has been found only in the brain, the cervical spinal cord, terminal spinal cord, and the retina. I don't want you to read all the tissues here, but I want to put this slide up to impress you of the large number of other tissues from these same cattle which have been bioassayed in the same animals to show that none of these tissues listed contain infectivity. If this had been sheep with scrapie, we would have been expecting to find infectivity in spleen, in lymph nodes, possibly in peripheral nodes that in the clinical phase of disease and cerebrospinal fluid.

But in the context of tallow, I want to draw particular attention to some issues and also in regard, for tomorrow, to gelatin. Midrum fat, which is the actual fat around the mesentery which is a high quality fat, was tested and shown to contain no detectible infectivity. It would equate with one of the depots of fat mentioned in the Scientific

Steering Committee's judgment that that kind of fat is okay.

I draw attention to the fact that skeletal muscle, mammary gland, blood and blood components do not show detectable infectivity. Neither do semen or embryos. In the context of gelatin, neither does skin, neither does bone -- oh, bone marrow. Here we are, bone marrow. None of those tissues have shown detectable infectivity in clinical cases of BSE.

This summarizes what David has just spoken about, that with rendering processes you can have effective processes and ineffective processes. The ineffective ones produce infected meat and bone marrow if they're spiked with BSE brain material, but the tallow derived from them or from the effective processes shows no detectable infectivity under experimental conditions. And once we're at it, it's convenient to get it out of the way for the purpose of a summary at the end that in 1994, as David mentioned to us, in regard to BSE spiked rendering material and rendering processes, continuous vacuum and one form of continuous atmospheric rendering system was banned in the European Union. Now, as a result from the scrapie

study, the only system available for rendering waste in the Union is 133 degrees Centigrade, three bar for 20 minutes or equivalent.

The important part of the tissue infectivity studies relate to what happens during the incubation period of BSE. We were fortunate in having the results of the work of Dr. Bill Hadlow, internationally famous veterinary neuropathologist, who did studies in sheep scrapie in regard to natural disease in Suffolk sheep and in goats. It's from that data that we first constructed our offal bans in the UK, but that's now been overtaken by results that we have from conducted pathogenesis studies in cattle. The objective is listed here.

The design of the study was to have 30 calves dosed orally at four months of age with 100 grams of brain and there were ten undosed controls. Two points to make about this. Firstly, the dose was very large, and secondly, this was unprocessed brain material, not rendered brain material. So, the challenge was enormous. Three challenged calves and one control were killed at four monthly intervals approximately commencing at six months of age. There was some slight adjustment as the experiment went on to that interval. From each of

the kills, we collected a range of tissues, some frozen for inoculation and others for other purposes.

This is the current result of this study which is still incomplete. The interval post-challenge is listed in months here. The green period, no kills were done at this time but this was the first time that we saw onset of clinical disease. Any animals that lived up to this age, every single one -- in the experiment had clinical disease. Remember that the incubation period in the natural disease is on average five years and this was two years quicker. So, I think that also tells us something about the infectivity of the brain compared with the meat and bone marrow.

Now, clinical signs, as I say, were detected from 35 months onwards. As with the other TSEs, it's not unexpected that you find infectivity in CNS tissue shortly before or around the time of clinical disease occurrence. You see this is shown -- this brain pathology, there is brain infectivity in the caudal medulla, in the spinal cord. The dorsal root ganglia, I'll come to in just a moment, and various other ganglia. Importantly, and we'd recognize this in 1994 in the study

conducted by Gerald Wells and colleagues at CVL, that the distal ileum showed infectivity from six months post dosing up to 18 months post dosing and again, from 38 to 40. This gap in the middle is not yet fully explained.

What was important was this recent result of finding infectivity in the dorsal root ganglia which resulted subsequently in the British Government removing bone in meat for consumption. That meant such things as T-bone steaks and rib steaks could no longer be consumed in the UK, not even from imported meat from any country in the world. That was really for control purposes. It was not the advice of the SEAC. We provided options for the government to take, one of which was the one they adopted. But we also provided lesser options because we considered the risk was extremely small. Tomorrow -- and I'll show this slide again tomorrow -- we noted that there was infectivity found in bone marrow, but this experiment is not possible to interpret at the present time.

So, we now come to control. The principles of the control, firstly in regard to protecting animals and man from BSE, is to eliminate or reduce exposure to a level below which disease

can not occur. We can not prove a zero risk. This is a very important concept.

It's convenient to consider controls in the context of animal health and also separately, in regard to public health. I'll deal with animal health first. I'm not going into any detail in some of the less important points relevant to today, but concentrating on the major control measures. In 1988, the disease was made notifiable. Suspect animals had to be restricted to farms and pregnant cattle imminently parturient had to be isolated in case there was any potential for maternal transmission. The main control, perhaps the only one, if it could have been effectively adopted from the word go, would be to have no ruminant protein in ruminant feed with certain obvious exceptions such as milk. So, this was the control which was hoped to be effective from a very short time after its introduction.

The second control was applied after we discovered that we could transmit BSE to pigs when we inoculated them intracerebrally. This would protect other species other than man, who is already protected because this ban had been in place since 1989 for human consumption purposes. As David has

shown, the animals that were born after the ban, at this point, none of these cases that are over here should have actually existed should that ban have been perfect. Unfortunately, it wasn't. The first short period probably was due to feed still in the supply chain, that the others were still being exposed right up until 1994, the so-called "born off the ban animals."

This histogram is for just six months because the ban only came in July of that year and it's conveniently and happily declining, but it's still noteworthy. We've had six cases of BSE in that cattle born in 1994. That's quite a long time after the ban. I won't go into the detail, but this was attributed to the cross contamination of ruminant rations first of all by porcine and poultry rations which, up until 1990, could legitimately and legally have contained meats and bone meal potentially carrying infectivity, and subsequently by cross contamination as a result of the offals ban, itself not working 100 percent either.

The feed ban has been amended and adjusted and refined over the period of time. It started as a ruminant protein-to-ruminants ban. Then in 1994, it is a mammalian protein-to-ruminants

ban which was already operative, actually, in the UK because we had mixed species raw materials. But this was applied by the European Commission to all member states. In 1996 in the UK alone, mammalian meat and bone meal was forbidden to be fed to all farmed animals, horses and fish -- a very, very severe ban. The question is, how do we police it?

I don't want to go into the detail here, but this summarizes amendments and adjustments and dates when they took place for various things. I want to draw your attention to this particular item here, the ELISA test which had been developed in one of our veterinary investigation centers to identify specie-specific materials in imported meats and so on originally to stop people selling imported kangaroo as beef and so on. We had to check it. So, this ELISA test was adopted for use to detect mammalian species protein in meat and bone meal.

Now, this is currently done. We do several thousand tests a year and all these tests are reported to the public -- if you could just show this to the audience, please? Please, just show it to the audience -- in our BSE Enforcement Bulletin which gives a description of many of the things I've already told you about and the results of those

ELISA tests. Any positive tests are investigated very thoroughly and none has been reported this February to be positive in any case. Some of the positives are false positives due to particular cross reactions resulting from plant protein. So, there's a lot of research required to get this test to work well, but we're very happy with it now. It does demonstrate to the public that there is safety in cattle feed.

I mentioned this one earlier. Next slide, please.

Now, human health risks, instead of animal health risk, could potentially arise in respect from BSE from the consumption of specified risk materials, mechanically recovered meat from sheep, from gelatin, collagen, tallow, pharmaceutical, biological, medical, cosmetic products containing bovine material from medical devices in similar way, or from occupation. Clearly, we're not going to discuss many of these things today, just this little group here: tallow and meat and bone meal. So, in regard to public health, it is really quite simple. As a result of the initial committee, the Southwood Committee, advice was given that all animals, cattle, suspected

to have BSE should be removed from all food and feed chains. So, they were compulsorily slaughtered. They were compensated for, and the animal was totally destroyed other than the brain which was used for diagnostic purposes. Then the residue was destroyed.

The second control, a very important one, was the specified bovine offals ban, or SBO ban. This was to protect the public from exposure to infected tissues. We did at this time produce this list from the knowledge that we had from Bill Hadlow's studies and his colleagues in scrapie. This offals were regarded as the following. The brain and the spinal cord, the tonsil, thymus, spleen and intestine from all cattle over six months of age, and the intestine was from the duodenum to the rectum. That meant that the tripe organs anterior to that and the tongue and so on were regarded as safe. This ban itself was modified in the light of new information. Firstly, we had the ban for humans in '89, then moved on to all mammals and birds in 1990. Then from 1994 to 1997, there were a number of extensions and I'll deal with those now.

It may surprise you that before BSE,

there was already a significant offals ban in regard to use of them in uncooked meat products. So, none of those offals I've just listed, and a whole range of other ones, were permitted in uncooked meat products anyway under the existing law and had nothing whatever to do with BSE. The exclusion was thymus which, curiously, under our law, is regarded as meat. So, you could have it in a sausage if it was thymus and you had a ten percent meat content, it could be theoretically 100 percent thymus and regarded as meat. At that time, we had a potential concern because it is a lymphoreticular tissue.

However, in regard to calves, we did not consider there was a risk factor for calves under six months originally. But as a result of that pathogenesis study where we found infectivity in the distal ileum, in 1994, no intestine or thymus gland was allowed even from calves under six months. So, we had the SBO ban for cattle over six months in '89.

In 1995, we prevented skulls being utilized and this was because what was being done by the industry was to remove the brains. The brains would go for SBO and the residue of the skull would go for rendering and then get back into feed. But

if the rendering system did not destroy infectivity, the residual brain material that could have been left in the skull, and of course the eyes which, at that time, we did not recognize as being infected -- and no studies had been done on them in scrapie -- we thought it was a good idea to take the skulls out. We were also concerned from public health issues in regard to spinal cord getting into mechanically recovered meat. Therefore, this was also removed by not allowing vertebral column from cattle to be utilized for manufacture of this commodity.

In March 1996 after the new variant was announced, no cattle over 30 months were decided by the government to be consumed. This was not the advice of the SEAC. SEAC advised that all meat from these animals over this age should be deboned, but the government chose instead to not consume anything. That became the law. There were also, on SEAC's advice, heads excluding the tongue -- unless it was contaminated, the head would be condemned as well. As a result of finding the infectivity in dorsal root ganglia which could be in such things as T-bone steaks, it was decided again by the government that no bones should be used. As I

mentioned earlier, the SEAC gave the government three options and this was one of the options. But there were lesser options because we considered the calculated risk to be extraordinarily low.

The question of infectivity in the bone marrow, as I said earlier, was uninterpretable and I think had we only had that study -- but don't forget that that was only found in clinically affected animals anyway -- we probably would have held fire on this. But nevertheless, at present, we're not allowed to eat cattle over 30 months and even from those, not bone-in or meat on the bone.

In the EU, we're subject to various controls which apply to all member states. There's the feed ban I've already mentioned, the rendering changes, the specified risk materials ban which was mentioned by an earlier speaker this morning, Dr. Bailey. This one was to have been applied last July. It was postponed until January, again postponed to April, and it is now postponed for some date into the future with possible modifications. I won't go into the detail. It operates, nevertheless, in the UK and in France at the moment, and possibly in some other countries.

The most important issue which has got

nothing to do with science, as you mentioned, for public confidence reasons, export of live cattle and products excluding semen and milk from the UK was established in March 1996 and that is still our current position. We now have the agreement with the Commission and the member states to reestablish exports and it looks very favorable that we can start this with Northern Ireland meat very shortly, and hopefully by the UK sometime soon afterwards.

The specified risk materials have already been mentioned: the skull including brains and eyes, tonsils, spinal cord from cattle, sheep, goats over 12 months of age. The sheep and goats is to protect from the possible risk, total hypothetical risk of there being BSE in sheep as distinct from scrapie in sheep. But it also has an animal health protection measure in regard to meat and bone meal in other member states because if there was scrapie infectivity in brain and the meat and bone meal was getting into pig and poultry feed, there's clear evidence that there must be cross contamination of ruminant rations and theoretically, the scrapie could get back to sheep. We wouldn't want that either. So, this was to adopt a risk reduction rather than a risk elimination policy from

the European Union's point of view. The spleen was taken too because that is known to be infected both in scrapie and BSE, or experimental BSE in sheep. The vertebral column of these three species was prohibited to make MRN.

The last summary slide -- and I'll take you through it if you'll just bear in mind that I picked up the wrong slide. I have altered this. This should read "affected" here, not just "infected." How we start is with cattle of all ages which are healthy, susceptible and uninfected with the TSE agent of any sort. Calves and all products present no hazard and therefore, no risk. Everything would be safe in common parlance. If we feed infected feed, cattle could become infected but remain healthy. The problem is determining which ones are infected and which ones are not, and we can not do that. From such cattle, milk and meat is regarded as safe and present a negligible risk providing there are various controls in place.

In regard to the specified bovine materials, there is a hazard, a high risk. These need to be rendered or incinerated or buried. They then present a negligible risk. If the healthy cattle develop clinical disease and become affected,

then there is compulsory slaughter and incineration, thereby converting them into the green for go, negligible risk category. In this way, the problem that you start with here, hopefully, disappears.

With that, I finish. Thank you very much for your attention.

(Applause.)

CHAIRMAN BROWN: Thank you.

We now have up to a half-hour to query and question anything we have heard this morning from the committee.

Ray?

DR. ROOS: I had a question for Dr. Bradley.

CHAIRMAN BROWN: Oh, incidentally, let me reiterate that David Taylor and Ray Bradley position themselves behind microphones around the Committee table.

Yes, Ray?

DR. ROOS: Yes, I wasn't quite sure how tallow fit into the ban with respect to animal feed.

DR. BRADLEY: There is no ban on the use of tallow.

CHAIRMAN BROWN: Clean.

Other questions? Yes?

DR. FRANCO: Ray, I wonder whether or not you would consider -- and I know how cumbersome it is -- using some comparative analogies based on ILSAs that are less than 100 grams?

DR. BRADLEY: Right. We have done some attack rate studies in cattle. In this study, we had 40 cattle, ten in each of four groups. One group was challenged orally with three times 100 grams. That's 100 grams on three occasions. One group with a 100 grams, the third group with ten grams, and the last group with one gram. I can tell you that although this study is incomplete, that all four challenged groups have succumbed to BSE.

The important message from this study, remembering that it was brain material that was used rather than meat and bone meal, that assuming the rendering procedure produced -- or the drawing procedure produced no reduction in titre, the actual amount, the physical volume to look at, of the amount of tissue necessary to produce BSE in about three years, or three to four years after all dosage of, let's say, about .1 of a gram of the dried brain material -- well, it is .1 of a gram. In other words, if you reckon that brain when you dry it weighs about -- nine-tenths of it is gone and

reduced to .1 of a gram of dried product, this very small amount is not something that anybody could control under farming conditions. When you would be talking about we need 2.5 kilograms to infect a cow, then this would be readily possible to control. But such a small amount which is presumed from the study showing that one gram will produce BSE three to four years later, it's quite a remarkable piece of information. Of course, we don't know the dose of meat and bone meal that will do that, only raw brain material.

CHAIRMAN BROWN: Yes, Leon, go ahead.

MR. FAITEK: In one of Dr. Taylor's slides, you showed various temperatures and various titres, and the numbers were something like 10^9 and 10^8. Were the titres remaining after subjecting the sample to those temperatures? Those weren't reductions in titre, were they?

DR. TAYLOR: These were the starting titres. We customarily, in the types of processes, describe -- lose five, six, maybe even seven logs to infectivity. We would lose in these scrapie base studies about five or six logs of infectivity by the autoclaving procedures described.

One thing to say is that the titres

quoted, which at its highest 10^9.something may seem extraordinarily high in view of the titres of BSE infectivity we talk about when measured in mice, which can be up to maximum, say, $10^{4.5}$. But of course, what studies have shown at the Central Veterinary Laboratory is that the differential between the cattle and a mouse biopsy is about 1000-fold. So, when we talk about 4.5 logs of BSE infectivity measured in mice, that's probably 7.5 to 8 logs if measured in cattle. And the scrapie data I was talking about were from hamster-to-hamster with no species barrier.

MR. FAITEK: And you say that reduction was about four to five logs from those levels after subjecting them to those temperatures?

DR. TAYLOR: Yes, about five-plus logs would be the customary experience in these types of autoclaving experiments, yes.

CHAIRMAN BROWN: I think this would be a good point for me to interject one point that I have always considered important and that is the mental set that we adopt for discussing results that indicate reduction of infectivity. That is to say, demonstrating that you start with a certain level of infectivity and then you detect a certain lower

level of infectivity. That is to say detectable infectivity. That mental set and that experimental design as opposed to being able to conclude that there is no infectivity.

I use as an illustration of this, David's paper on the BSE rendering. If my arithmetic is correct -- and David, you'll have to keep me honest in this -- I see that you, in various of the rendering processes, rendered a total of 250 kilograms of material. That is a process that was tested was 250 kilograms of material. The total amount of that material that was assayed in any given batch was somewhere between one and two grams. So that, if you found infectivity, that is a very satisfactory result in terms of having something precise. If you did not find infectivity, which was the case in at least four of the processes, the amount of the total sample that was actually assayed was one-millionth.

Well, if you assay one-millionth, it gives you a certain leeway to imagine that that "absence" of infectivity in that one-millionth leaves some room for the possibility that in the other 999,000 of the total specimen, there could turn up a few infectious units that you would not

detect. This is not a critique, or I should say a criticism of these experiments which were excellent experiments, but you must not just cavalierly conclude that from these experiments you have shown the absence of infectivity in any specimen that you have sampled.

Further questions? Ray? Wait a second.

Larry, you had a question before, did you?

DR. SCHONBERGER: Basically, just a point of clarification on David Taylor's point about the stopping of solvent extraction in the UK.

Did I understand you to say that solvents can fix the BSE agent to protect it from heat, but that your assessment of the overall effect of stopping solvent in the UK was to possibly increase the titres in the end product by one log, or something like that? Could you clarify that again?

DR. TAYLOR: Yes. The overall conclusion was not that the titre was actually enhanced as opposed to reduced, but that on average, we lost about one log through the whole process. But rather interestingly, there were hints and I would suggest some bits of evidence that on some

parts of the process, you could show the use of heat, per se, was actually causing the degree of inactivation that you had measured rather than heat plus solvent. There was even a suggestion that the effect of solvent was sometimes sparing the agent from inactivating effects of heat. Nevertheless, overall, there was about a one log loss of infectivity for most of the processes.

CHAIRMAN BROWN: Ray?

DR. ROOS: Yes, just to follow up on a comment that you made about Dr. Taylor's studies and the potential limitations here. I got the feeling that a number of the transmissions involved rather long incubation periods. So, the other issue that is a somewhat unavoidable one is, if you don't get infectivity and the animal doesn't come down, does that mean that there isn't infectivity? Or does it just mean that the incubation period is in excess of the life span of these animals, since it certainly was being approached? So, this is another issue with respect to these assays.

DR. TAYLOR: The questions which you ask, we were certainly aware of when we started not only these experiments but a large number of studies relating to BSE. With the fullness of time, we have

come to appreciate that there does seem to be pretty well a maximum incubation period that you can get under various circumstances on which we can usually measure. But as you rightly comment that as experiments progress further and further into time, you do suffer from increasing intercurrent losses of animals which, of course, reduces the sensitivity of your assay.

But the other point I would make is that all animals, not just those displaying clinical science -- this is mice -- even those negative at the end of an experiment are subjected to histological examination of the brain. Now, the perfect situation would be to take those that are negative and passage their brains and spleens back into new animals to absolutely prove there's nothing hanging around there. But we just have too many experiments to afford ourselves that luxury.

CHAIRMAN BROWN: And of course, you'd have to do that with 24 million mice.

Ray?

DR. BRADLEY: If I may, Mr. Chairman, I'd just like to come back on the reply I gave to the question on tallow. I said that there wasn't a restriction on tallow. By that I meant that tallow

coming from our currently under 30 month old animals, of which have been caused fit for human consumption, no problem, that there is no restriction. But I need to emphasize the fact that tallow prepared from specified risk materials, number one, or all the cattle that are over 30 months of age, that is forbidden to be used.

I want to give you some figures to show the extreme importance of the economics of this. To date, we've killed over two million cattle over 30 months and of their productive life, whatever that may be. This has produced something like a quarter to a third of a million tons of meat and bone meal from those which were rendered, and something of the order of 158,000 tons of tallow which is currently stored pending disposal. This can not be used for anything and it has to eventually be incinerated. We've got ideas of how to do this, but it's not actually yet been done.

So, just to clarify, tallow from the animals under 30 months, no problem except we can't export it. There is no European Union ban on tallow. It's purely on meat and bone meal.

CHAIRMAN BROWN: There are rumors that this tallow will wind up as heating fuel for Windsor

Palace. Is there anything to that?

DR. BRADLEY: Correct. We have done studies to, I'd say collectively weigh -- this is not my institute, but collectively in the UK, have done studies to demonstrate the risk factor from burning this as a fuel in power stations. The risk factor is extraordinarily low, much lower than we would normally experience in anything that we do in normal life. I think it suggested -- I heard quoted that you might have to consume 2.5 kilos of the flu ash from a chimney from these in one go to get one potential lethal mouse dose, or something of that order.

So, it's safe. For practical purpose, it is safe to do this and the best way to get rid of it. Unfortunately, the power stations want an indemnity from the government to make sure that that statement is correct in actual practical terms, and there's an impasse at the minute.

CHAIRMAN BROWN: Yes?

DR. BURKE: A question and clarification from Dr. Bradley.

You mentioned that bone marrow and skin has not been found to be infectious from the BSE, where it is in scrapie. How were those assayed?

Were they assayed back by passage into susceptible bovines, or were those assayed in a mouse assay?

DR. BRADLEY: Into mice.

DR. BURKE: So that, that may well reflect the fact that it's an insensitive assay for detecting the presence of the agent?

DR. BRADLEY: All it can tell you is that the titre that is present is at least 1,000 times lower than it is in the brain.

DR. BURKE: But in the comparison of scrapie to bovine, it doesn't really say that there's any significant tissue distribution difference between the two species?

DR. BRADLEY: Well, I would beg to differ there.

DR. BURKE: Okay, well, that's the clarification I'm after.

DR. BRADLEY: Yes, because in BSE -- and there's another experiment I need to just mention briefly. We haven't been able to find any infectivity in the spleen, not even by bioassay in cattle and equally with lymph nodes as well. I have to say that those studies are incomplete. In other words, the cattle are still alive well after the incubation period for the brain tissue from the same

source and which, of course, did transmit to the cattle very quickly. I think it's now about six years.

The question is, when do you draw the line and say it's a negative study. We haven't got a dose response curve for cattle yet, even from brain tissue. So, it's difficult to come to a conclusion. But I think we've generally accepted that seven years is an acceptable, reasonable time limit if no disease has occurred in that time, particularly by an IC route. This was not an oral route.

DR. BURKE: Sure.

DR. BRADLEY: So, it's a very severe challenge. So, I think there is a difference between, first of all, sheep scrapie in cattle. There seems to be a difference which could be reflected for various reasons between the experimental pathogenesis results and the ones in the actual field epidemic. There is also a difference between BSE in cattle and BSE in sheep. If we feed even sheep, does one sheep in the world so far think I'm saying, David, that has been fed BSE after six that came down with BSE. In that animal, there was infectivity detected in the

spleen. But no other tissues were examined so we don't know.

DR. BURKE: Can you say how many animals so far have been assayed, or there has been tissues assayed in the bovine bioassay?

DR. BRADLEY: How many tissues?

DR. BURKE: Yes, how many animals where you've looked at bone marrow or skin or some of the other areas that are thought not to have --

DR. BRADLEY: No. Well, those experiments are just being set up or only just started. I couldn't give you figures. But some of the important tissues which your Committee and the SEAC's would advise would be done are being done. I couldn't list them here and now, but that could be given to you.

CHAIRMAN BROWN: A more specific question, Ray, in a given assay in cattle where the bioassay of infectivity from a tissue in a cow, whether experimentally or naturally infected, is assayed in other cattle, how many cattle are inoculated for that bioassay? Let us suppose you want to find out the infectivity in the spleen. How many cattle are inoculated with spleen?

DR. BRADLEY: I think it was a

relatively small number like three or five or something of that sort. I can't recall.

CHAIRMAN BROWN: But it would be at least --

DR. BRADLEY: Do you know, Will?

DR. HUESTON: It depends on the tissue, right, because the embryo work is a much larger number, that placenta work was -- I mean, there's a whole range --

CHAIRMAN BROWN: Yes, but it's apart from reproductive tissues or tissues assayed for information about reproductive tissue. It would be three, four, five animals per specimen?

DR. BRADLEY: That sort -- exactly.

DR. ROOS: And would each one of those animals be for a separate spleen? In other words, when you say there's no spleen inactivity, I mean, you're --

DR. BRADLEY: No, we pulled spleens, pulled lymph nodes, and pulled brains from five separate individual cases of field BSE, all of which were confirmed.

CHAIRMAN BROWN: Would you agree that it's a fair summary to say that in view of rather similar, overall tissue distributions of infectivity

in most spongiform encephalopathies, that as yet, distinctive differences that seem to be appearing in BSE may or may not in time turn out to be distinctive differences. And that you would be very cautious writing off virtually any tissue in a BSE infected animal as risk free, at the moment?

DR. BRADLEY: I think it's a question not of yes/no, is it there, but how much. I think the how much is a very important question. I'll have to say also that when the studies were done in sheep, from sheep by Bill Hadlow and colleagues, they used mice. There's a species barrier there, too. So, actually, if you assayed those in the requisite kind of sheep of the right PRP genotype, the maximally sensitive animal, it may well be that you would find infectivity in other tissues.

CHAIRMAN BROWN: It might be. It might also be that the species barrier, so-called, between sheep scrapie and mice is considerably lower than that between BSE and mice. I don't think there's any systematic study which shows that species barriers are uniformly -- form uniform barriers.

David?

DR. TAYLOR: Just one comment, Paul, and that's just to say that in some cases where we have

clear evidence of clinical scrapie in sheep, classical symptoms, PRP staining in the brain, we do sometimes don't get most transmission.

CHAIRMAN BROWN: Yes, that's true for CJD and some labs have success, some don't. The species barriers are tricky, dicey things.

DR. BRADLEY: I think one of the other interesting features is the recent study that Randall Cutlip has reported in the USA between scrapie in sheep experimentally transmitted to cattle, and then from the cattle again to cattle. The incubation periods, and judged only upon that, were very similar as he points out in his paper between the first and second pathologies.

Now, I think I would hesitate to say that it indicates that there is no species barrier because we don't know the titres of the agent. But nevertheless, there's a possibility that there's a pretty low species barrier between those two species.

CHAIRMAN BROWN: Oh, Larry, okay.

DR. SCHONBERGER: I wanted to clarify the testing on the various rendering procedures. One of the rendering procedures you found was better than the others, is that right, because you had

negative tests? This was at pressure cooking at 133, three bars, 20 minutes, is that right? But didn't we hear before that that process would denature the proteins and that you wouldn't end up with a satisfactory product?

CHAIRMAN BROWN: Yes, I inferred the same thing, that that particular procedure which, of course, the experiment was done primarily for meat and bone meal rather than for tallow, is incompatible with quality tallow. Is that correct?

DR. SCHONBERGER: Is that correct? That's what we want to find out.

CHAIRMAN BROWN: That's the implication.

DR. TAYLOR: My understanding is that the meat and bone meal is okay, but tallow subjected to that sort of process is certainly not high quality tallow. It doesn't end up as a high quality tallow.

CHAIRMAN BROWN: Linda?

DR. DETWILER: On that same -- you had said that the European Union had put into place that rendering process of 133, three bar, 20 minutes, but there's reports out of the Commission that not all countries have implemented. What would be the percentage that have actually gone ahead and changed

their whole rendering system over to that? Do you have any idea?

DR. TAYLOR: Well, the UK has not, simply because as Ray explained, we're now banning protein feeding to all farm species. I had heard that, for instance, the French were digging their heels in. But perhaps Ray knows more about the European reaction to this, or you may not want to tell it.

DR. BRADLEY: I think in France at the time when the ban was coming forward, they did have plants that were not operating on that basis. What I think that they have done -- but I would reserve judgment. You have to clarify with the French authorities that they've used those plants that do not operate at 133, three bar, 20 minutes for processing poultry material.

DR. DETWILER: Would you say that this -- I mean, it's supposed to be throughout the whole of the Union. Has that been done, do you know? To your knowledge?

DR. BRADLEY: Well, yes, it's Commission decision --

DR. DETWILER: No, no, no, not the decision, the actual implementation.

DR. BRADLEY: Yes, it's got to be enacted in each individual country. I've found it personally very difficult to get extract from countries, even notable countries, the date upon which -- and the document which says "here is our law." I have it for France. France has been first class in this, but I haven't had it from some other countries. You could see in my list of dates down there, they just had the year but I haven't got firm, legal evidence in the form of a document saying it's an article or a law.

CHAIRMAN BROWN: Clarification back -- yes?

MR. LANGENHORST: Yes, just a little point of clarity. When I was asked a question earlier, my response was with the current cooking systems, you can't always accomplish that specific process. The batch cooking system is the only one under which you can have all three of those happen. Or you can go through a continuous cooking process and then treat the meal afterwards. There is degradation to the amino acids in the proteins also. That was just done in the US and that has been shown. So, there is degradation of both the tallow and the protein.

As far as Linda's question, "has it been implemented throughout the EU?", the answer is no, it has not.

CHAIRMAN BROWN: But I still don't understand. You're not disagreeing with the notion that 134 degrees Centigrade degrades tallow?

MR. LANGENHORST: It does.

CHAIRMAN BROWN: It does. So, it's simply not a practical thing even to think about with respect to processing tallow?

MR. LANGENHORST: I'd leave that up to the people that buy our tallow to tell you, probably. We're not going further than that, you know, in our part of it, but the people that would use tallow could be able to answer that question much better.

CHAIRMAN BROWN: Are they here? Are the tallow users here?

MR. LANGENHORST: The people this afternoon will be speaking on that, yes.

CHAIRMAN BROWN: You might want to answer that specific question, "have you ever used", "do you know about the qualities of tallow subjected to temperatures of at least 132 degrees Centigrade?" Not just an opinion, but evidence.

Leon?

MR. FAITEK: Even more than that, bearing in mind the difference between attenuation and elimination -- and we're talking about 130 or 140 degrees C here, at one of our previous presentations we were told that the infectious agent was heated to some phenomenal number like 300, over 300 degrees C and there was still infectious agents present after heating to that temperature. In view of that, how effective does the Committee feel that 130 degree heating would be providing adequate safety?

CHAIRMAN BROWN: Yes, I don't think anybody is going to be able to give you a precise answer.

In view of this question that you raise, I'm reminded that Dr. Bob Brewer in the audience emphasized to me something which may have escaped the attention of other people. The rendering process is exposing the material not to autoclave type conditions, but to dry heat. It's a heat transfer from steam, wet heat, to material. So, basically, it's like putting it on a stove in a pot in terms of the heat, the type of heat that is being used. We already know that dry heat is incredibly

less effective in inactivation of these agents, or any other agent for that matter, than is wet heat. So, atmospheric pressure using temperatures even of 132 or 140 are not anywhere near as heating to these temperatures under autoclave conditions more than a single bar, more than atmospheric pressure.

So, you're quite right. We don't have information about zero infectivity. The idea of reducing is the idea that is going to have to be uppermost in mind. Even a temperature of 121 reduces the infectivity. And as I think we are becoming aware from the whole BSE problem, it is possible that very small reductions can have very large results.

Other questions? Barbara?

MS. HARRELL: Okay, Mitch Kilanowski made a statement that edible tallow does not contain head and spinal cord. Are you saying that because those raw materials are not used in producing tallow? What brings that to mind is that I remember I think about a year, they said that spinal cord was found in ground beef. I was just trying to see how you could make an emphatic statement.

DR. HUESTON: At this point, I understand that it is being taken out.

MS. HARRELL: Is being --

DR. HUESTON: Being taken out.

MS. HARRELL: -- not has not been?

DR. HUESTON: Heads are being taken out and spinal cords, as I understand it.

MS. HARRELL: Thank you.

CHAIRMAN BROWN: If there are no other questions, we will now take the lunch break. It is 12:00 noon exactly, and we will reconvene at 1:00 p.m.

DR. FREAS: There is a table downstairs reserved for Committee metiers. If the Committee members would sit there, it might speed service and you'd be back on time. Thank you.

(Whereupon, the meeting was recessed at 11:55 a.m., to reconvene later this same day.)

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

12:58 p.m.

CHAIRMAN BROWN: Good afternoon. We are introducing this afternoon's tallow derivatives presentations with an opening talk by Dr. Gerald Pflug who, according to the program, represents the Soap and Detergent Association.

Is that correct, Dr. Pflug?

DR. PFLUG: Good afternoon, ladies and gentlemen. My name is Gerry Pflug and I'm president of the Soap and Detergent Association.

The association was founded in 1926 and is a North American based trade association whose members manufacture in the United States, Canada and Mexico. The Association today has approximately 150 member companies representing those that manufacture the cleaning products such as Proctor & Gamble, Lever, Colgate, Amway, Dial, and Reckitt & Coleman to cite a few; the raw material suppliers such as Shell, Candia Vista, Union Carbide, Steppon and Witco. Also included are the oleochemical producers and finally, the packaging manufacturers.

The Association represents well over 90 percent of the cleaning products produced and sold in North America for both household and industrial

and institutional uses. The association has four divisions. The first and the largest is the Technical and Materials Division which consists of product formulator companies, as well as raw material suppliers. The second division is the Household Division which consists primarily of household products companies. The third division is a division which consists of companies who supply the industrial and institutional needs of industry, and finally, the Oleochemicals Division.

Approximately 18 months ago, the SDA under the leadership of its Oleochemical Division conducted a survey of its members to document the methods and conditions used for the feedstocks to produce oleochemicals. The SDA worked together with the FDA to develop the ultimate questionnaires that were used in this survey. The results were tabulated by an outside consulting firm and overseen by SDA general counsel. In August of 1997, the initial document representing the results of the SDA survey was completed and submitted to the FDA. I think you've all seen that. A follow-up meeting was held with the FDA to discuss the document and identify further information which was needed. A supplement to the original document was submitted in

March of 1998 and today, an addendum to the supplement is available.

This survey represents between 95 and 100 percent of the major uses of oleochemicals in the United States. It is the belief of SDA and its members that the data generated and presented with regard to temperatures, pressures and times demonstrates how the industry helps assure the safety of oleochemicals produced in the United States . They are representative of typical operating conditions in the industry. We welcome any questions you may have with regard to the survey, its conduct, or its results.

This afternoon you will hear presentations from the following. Dr. Charles Green of Witco, who is director of Regulatory and Toxicology for the Oleochemicals/Surfactants Group who will discuss feedstocks, the overview of the US oleochemical industry, and production processes. He will be followed by Dr. Philip Merrell of Mallinckrodt who is a research associate in the Specialty Chemicals R&D Department. He will discuss the manufacturing process of magnesium stearate. Next will be Stan Gorak from ICI Americas who is manager of Quality and Process Chemistries. Stan

will discuss the manufacturing processes for polysorbates , Dennis Walker of Proctor & Gamble who is regulatory manager for Proctor & Gamble's Chemical Group will discuss oleochemical safety in the United States. Finally, Dr. Frederick Bader of Centicor, VP for worldwide operations will discus the safety of pharmaceuticals.

We thank you for the opportunity to present our findings. Thank you.

CHAIRMAN BROWN: Thanks very much, Dr. Pflug .

Dr. Green has a block of one hour. If he chooses to use it, that's fine. We won't interrupt him. Following his presentations, plural, we'll probably have time for one or two others before the break. We shall see.

Dr. Green?

DR. GREEN: First of all, I want to thank you for inviting me to speak here. I hope that possibly some of the things I say might answer some of the questions that were asked this morning. I'm going to try to elute to some of them in further explanations that would give you a clearer understanding.

The safety of tallow and tallow

derivatives cited in the December publication of Journal of Veterinarian Records by Dr. Taylor is going to be what we consider our base to make comparison against. Dr. Taylor's publication demonstrated a minimal margin of safety needed for production standards was 20 minutes with a temperature of 133 degrees C and three bars, in which we are very generously going to call that 48 psi, pounds per square inch. In industry, we will use terms like psi versus bars because of the way the computers are programmed, we need the flexibility and trimline analysis to use a much more flexible mechanism. But I will always give you both comparisons. This is pretty much true throughout the world.

One of the things that I would like to point out is that Witco is a multinational company. We have plants not only in the United States. We have plants in Europe and are presently putting plants in Asia. This is very true of all of the multinational companies have plants all over the world. One of the things that you might want to be aware of is plants do interplant transfer of products where they may not have all the equipment that they use in full production in one location.

They may do partial production in one location and move it to another location. Specifically to that reference, I will address a question that has come up on why tallow would be imported into the United States . There's a explanation for answering that question and why.

The oleochemical industry will show that their method of processing tallow and then taking the processed tallow into derivatives significantly exceeds the minimal standard as set by Dr. Taylor's publication. The Soap and Detergent Association survey reflects representation of nearly all the industry, multi-step processing under harsh conditions and we are going to emphasize time, temperature and pressure throughout the entire presentation. I also want to state that Witco processes not only tallow, but we process vegetable oils, and fish oils, and everything. It's the same set of conditions for processing. It's the same type of equipment. It is identical irrespective of which triglyceride you're using.

I'm going to focus on various manufacturing procedures. In particular, I'm going to address saponification, hydrolysis -- we call it splitting, but that's a manufacturing term. In a

laboratory, it's called hydrolysis -- and transesterification. The three routes that tallow is converted into derivatives and refined into fatty acids and ester. We're going to talk about the operating conditions, routine and process quality testing. The processes presented will apply to both edible tallow and inedible.

Let me say this, in processing tallow, the equipment and the conditions are identical. You do not process edible tallow in the same equipment you process inedible tallow. They're kept separate. The rail cars are brought into the plants separately. They're not mixed up. You do not go through common lines, common pumps, common headers or anything at a plant. They are totally separate.

Tallow derivatives touch us in many ways, improving the quality of our life in drugs, cosmetics, food, food additives and hundreds of other uses. Tallow to us is just a building block, much like ethylene gas is to the plastic industry or crude oil is to industry, or you use it as a building block to make many, many down field derivatives . These derivatives are used in almost all facets of the market world. I'm going to focus on the issue here today of food and pharmaceuticals

and cosmetics.

Quickly, I'm going through this. This is just an edible versus inedible. It's a comparison of 1993 to '96. This is in millions of pounds . We seem to play around with tons and pounds, so I'm going to stick with pounds. I'm a chemist, so I prefer to stick with one term.

The consumption, this is edible products. It just shows the baking fats and others. This is just to show there's a slight dip in this because of certain trends towards using vegetable source in certain market areas. This simply shows an overview. I'm only going to elaborate very quickly on it. It just shows the soap consumption is pretty constant. The feed consumption is a large portion in tallow. The lubricants and the fatty acids is pretty uniform.

This is a quick overview of how you have hydrolysis, or what we call splitting. When we mean splitting, we mean split the fatty acid away from the glycerin. We recognize that the predominant species are stearic, oleic and palmitic acids.

In transesterification, you're taking the tallow and putting methyl alcohol in there. You're converting it and doing a transesterification

straight through to the methyl ester. What we do then, and what is done then, you take the methyl ester -- the reasons for converting to methyl esters if you're analytically -- and you know anything about analytical labs, you want to analyze fatty acids, you make the methyl ester because you can get it down to the gas chromatography and you get a much cleaner separation.

The same is very true if you want to separate out high purity stearic, high purity oleic, or high purity palmitic. By having the methyl ester near distillation tower in the plant, it's so much easier to separate it. That is part of the reason why certain companies using methyl ester production in their transesterification because the next step they do after that is to convert the methyl ester, again by transesterification and reduction with hydrogenation to the alcohol. That' s how you get high purity stearic acid. This has its own derivatization after that. I'll touch that briefly, later.

Processing in our plants are computer controlled. Let me state this. Witco processes more than 300 million pounds of tallow every year. If you take the value of down time, maintenance on

equipment, that equates out to we process approximately one million pounds every day, 365 days out of the year. When we talk about processing in something of this magnitude, you have to have automated equipment and it's very large equipment.

Now, what we do -- and I said I would elute to a question this morning -- one of the first steps -- let me have the next slide -- I want to do an overview again on each phase, keeping in mind that we're going to talk about time, temperature and pressure. You'll see when I start through this, what that really means.

We're going to do hydrogenation. We're going to do hydrolysis distillation, the separation of the fatty acids, separation of glycerin, conversion of glycerin to US pig glycerin. Then we're going to derivatives and then we're going to means.

What we do first, we take the edible tallow and we do a partial hydrogenation on it before it is ever split. Now at that point, 1'11 show you how you can have importation of tallow into the United States. We are a multinational company. Our -- is here in the United States, but we have plants all over Europe. We have hydrogenation

equipment here that's much more sophisticated than plants in Europe. It is not uncommon for us to start a partial hydrogenation before we ship products to our plants overseas. The same thing happens when you have plants whose major facilities are overseas and they have plants in the United States . They start hydrogenation there and then import it here.

The way that's commonly referred to as hard tallow, soft tallow. What do you mean by hard tallow, soft tallow? Hard tallow is where you have hydrogenated out unsaturation, pushed it up to a pretty high extent. If you're going to convert it to fatty alcohols, you prefer stearic alcohol. So, there's a reason why you would do a partial hydrogenation before you imported it.

Now , when we start out, before we ever go to splitting the tallow, we do a partial hydrogenation. Here are your conditions. You' re going to take tallow -- oh, correction. I'm a little off here. This is saponification tallow. I'm going to cover that right quick like. Soap manufacturing generally is not done straight tallow. It's a blend. Generally, it's an 80/20 blend. Everybody has a little bit different in their

formulation. Your time is one to three hours. Your temperature is 100 to 115 degrees C, and your pressure is atmospheric. But you're operating under a caustic condition, at least 12 molar.

This is not the only way you can make soap. There are companies that take fatty acids and make soaps from fatty acids. Now, I will say one thing. In the chart on the board here where you have inedible tallow going to fatty acids, I can safely make this statement since I'm on not only the Soap and Detergent Association. I'm on other associations where all the fatty acid manufacturers in the United States are involved. Not one single company manufactures fatty acids from saponification. When you saponify it with an alkali, you've got a salt. Now, you've got to neutralize the salt off. You've got to filter the salt out. You do not do that. In the old days, it might have been done. Since 1980, nobody does that in the United States, not the fatty acid through saponification.

I think that the understanding of soap -- soap is not a single time where you just saponify it and you've got it. You do a saponification. You drain off so much of the glycerin. You saponify it

again. You drain off the glycerin. You go through a multi-step, multi-contact with alkali. You mill it. Then you blend back various components. There are certain things as waxes and so forth that added the soap to control the rate at which it dissolves. They put preservatives in it. They put bacterial agents, if that's the type of bar they're making, and what-have-you. So, all of this is a multi-complex system.

CHAIRMAN BROWN: Yes, Dr. Green, what is the pH of the solution?

DR. GREEN: The pH of the solution as it starts out would be over 12.

CHAIRMAN BROWN: Not quite 13, but over 12? Somewhere between the two?

DR. GREEN: Yes, yes.

Transesterification of tallow. The time in the transesterification is six to eight hours. The temperature is 160 to 170 C and your pressure is 25 to 75 psi. The reason you're doing it at that, methanol is very hard to keep in solution when you've got it that hot. So, you have to have that much pressure to keep the methanol where it will react.

Now, when you do the second stage where

you're going from the transesterification of the methyl ester to the subsequent alcohol such as predominantly seal or stearyl alcohol, you're going to have one to three hours. Now your pressure and your temperature is going to radically change. Your temperature is about 250 to 300 degrees C. Your pressure is 3,000 pounds to 4,000 pounds per square inch which is a radical change in time, temperature and pressure. This is the way that you do the transesterification.

Fatty acids and splitting. This is a process that almost everybody, not only in the United States but throughout the world, that uses this hydrolysis step uses this same procedure. You have tallow and steam, your three to four hours, and temperature is 248 to 271. Now, I've covered the entire manufacturing range in North America. Those set of temperatures will cover every person or every company that's manufacturing. The pressure will run between 710 and 730 psi. That covers all the pressures that are used in the industry.

You could have fatty acid in glycerin. Now you must distill the fatty acid -- what we call the tallow fatty acid. We're going to still that out into its components. Here is the time,

temperature and pressure used to do this. Your time is about 25 minutes in the distillation tower. Your temperature is about 249 to 254 C. I don't care what you do, that fatty acids distilled at the same temperature, so that's your range. Your pressure, you're going to do it at reduced pressure. You do it under atmospheric or increased pressure, you're going to have decompositioned products of your fatty acid. Now you have separated your stearic, your palmitic and oleic acids.

This is a typical glycerin distillation. You have crude glycerin when you split or separate or hydrolysis, however you want to call it -- you get glycerin plus water. Now you're going to separate the water from the glycerin. You can not do it in a single distillation. It's a minimum two stage, and in some instances, people have to go to three stages. This is the first stage where you go up to about a 95 percent distilled glycerin. Your time is approximately one hour. Your temperature is 161 to 171 degrees C. You're operating at a reduced pressure. You must not distill glycerin at atmospheric or increased pressure or you'll polymerize it. Or you'll start degradation of it, and one of the degradation products is acrolein

which is an alacromere.

Now you have distilled glycerin, but this is not USP grade glycerin. To get from distilled glycerin to USP grade glycerin, you go back up a distillation tower, 25 minutes, 166 to 171 C, and a reduced pressure, and now you'll have USP glycerin. This is how glycerin is made or distilled irrespective of its source. But this is exactly how it is distilled from tallow. Now I want to take and go from here to the derivatization section and show you the many types of derivatives you make and the conditions you're doing. But again, if you will notice, we have operated at very high temperatures either at reduced pressure or very high pressures, and we have had times far greater than 20 minutes as the minimum standard in Dr. Taylor's publication.

One thing you can do in derivatization is to take tallow, typical hydrogenated tallow, and convert it directly to the mono/diglycerides of tallow. There are two ways you make mono/diglycerides. I'm going to show you both of them. You take hydrogenated tallow, glycerin and a catalyst. Your time is about seven hours. Your temperature is 221 to 232 C, and you're operating at atmospheric pressure. This is a batch operation.

Now, prior to this, I was doing continuous operation. This is a batch operation. This is why your hours go up. You'll get a mono/diglyceride. You're operating in this condition. The catalyst, incidentally, is sodium hydroxide. So, you're putting a base catalyst in there. You've got glycerin. What you're going to do is put in excess glycerin so you convert a triglyceride to a mono/diglyceride and this is how it's done.

This is how you do it taking a fatty acid. Quite often, if you take the fatty acid -- you can take stearic or oleic for that matter -- and you do this. Again, you're using the fatty acid, glycerin and a base, catalyst. The base catalyst is sodium hydroxide. Your time is six hours. Your Temperature is 221 to 232 C. Your pressure is atmospheric. You get mono/diglycerides. These products are used both in pharmaceuticals and in direct food additives. They're covered under GRAS. Mono/diglycerides are commonly used in such items as no fat frying. A trade name might be something like Pam. These are the type things that you take the mono/diglycerides. There also, mono/diglycerides are then further processed. They're reacted with phosphoric, anhydride, and then neutralized with

sodium carbonate, That is a standard emulsifier for chocolate. That's what makes chocolate disperse into milk. Mono/diglycerides are also used in cake mixes and direct food additives in this line. The preferential of going to stearic versus -- that's predominantly done in cake mixes.

Glycerol mono oleate. Again, you generally take oleic acid and glycerine, about two-and-a-half hours, 204 to 246 C. The reason why that's such a wide diversity, it has to do with the speed agitation in the agitator, the number of baffles in the reactor. Different companies have different setups on their equipment. The pressure, again, is a reduced pressure. You don't want to polymerize the glycerine. You'll make glycerol mono oleate. Glycerol mono oleate is used as a direct food additive, and it's also used in some pharmaceuticals and topical applications. Glycerol mono oleate is also used in some of the topical applications . It winds up as a blocking agent to prevent diaper rash.

I want to briefly talk about some of the salts made from this. Dr. Merrell will discuss magnesium stearate made a different way. There are two ways you make metallic salts of stearic acid.

One of them is a fuse method and the other one we call precipitated. It's a difunctional method and he'll discuss that in detail in his part. I'm going to simply talk about the fused method for making stearates.

You wind up with the same product. It's just a matter of physical forms are different and surface areas are different. Again, you have about two hours. Your temperature is much lower but remember, this stearic acid has gone through some very high temperature than which it was prepared. Your temperature is about 74 to 88 degrees C and you're operating at atmospheric pressure. You wind up, in this case, with calcium stearate. Calcium stearate is used both in pharmaceuticals and it's extensively used in direct food additives. It's cleared under Title 21, CFR 172.860. I might also add that in the transesterification process, the fatty alcohols that are produced that are also approved for direct food applications under Title 21, CFR 172 paragraph.

This is zinc stearate. I use zinc for two reasons. Number one is, zinc stearate is applied in quite a number of topical pharmaceuticals for different purposes. Zinc stearate is used in

that way and zinc stearate is used in more indirect food applications than it is direct food applications. It's not only a mould release agent, but it's an excellent antioxidant. The manufacture, again, is about six hours. It's a batch process. You're operating at higher temperatures, 129 to 141 degrees C. Your pressure is atmospheric and you wind up with zinc stearate. These are both fused type operations.

I want to now get into how you make the fundamental basics for derivatives where you take the fatty acid that we've gone through the process of high temperature and pressure and time. Now you're going to go into some of the more downstream derivatives that are used in food applications and pharmaceuticals . This is ethylene glycol monostearate. This is a standard item that you quite extensively out there -- where you're going to react the glycol with the stearic acid. It's a batch operation; It takes about 16 hours. Your temperature is about 204 to 221 degrees C and you're operating at atmospheric pressure. You'll get ethylene glycol monostearate.

Now the way we quality control those operations is, you're running an acid number and you

want your acid number to go basically below one. That tells you you have very little free fatty acid left in the product. The way you control some of the other operations, you're always running acid numbers and sap numbers. Between those values, you instantly know how complete your reactions are.

This is how we take stearic acid and react ethylene oxide to it. Most of our systems are built like this in direct food additives. This is where you take ethylene oxide and you're going to react it with stearic acid. Now, this, again, is a batch operation under a very closed system and under a nitrogen atmosphere. You can not react ethylene oxide in the presence of any oxygen you have -- explosion. So, the system is totally under an inert atmosphere the entire operation. It takes about nine hours, 132 to 138 degrees C, 55 to 60 psi which is about four bars. You wind up with stearic acid hytoxilate.

Now, the number of moles of ethylene oxide can vary from very few all the way up to very many, depending on whether you're trying to balance an emulsifier system to be water soluble or oil soluble. Again, these are used in baking goods and very extensively so.

This is where you take stearyl alcohol and you react it. We're going to take stearic acid and go to stearyl alcohol. Let's give you a set of conditions. This is a batch operation where your time is 2.5 hours. Your temperature is about 320 to 340 degrees C. Your pressure is very high at over 4,000 psi. You wind up with stearyl alcohol and a catalyst. Obviously, you're doing hydrogenation to get to here. It's a metallic catalyst and it's very expensive and very difficult to do. It takes very specialized equipment to take these kinds of pressures and to handle hydrogenation. All companies that do that are very, very cognizant of the fact that hydrogen will explode very easily. Therefore, when I was alluding to a company in Europe whose headquarters is there and has plants in the United States, it's quite common for them to do partial hydrogenation and bring that product into the United States before finalizing it into their intermediates , I think if you really looked, you'll see where your importation from Germany comes from.

This is where you take cetyl/stearyl alcohol which is used in quite a number of topical applications and pharmaceuticals and you're going to ethoxylate it, basically the same way you do fatty

acids except the conditions are slightly different. Your time is about five hours. Your temperature is 135 to 140 c. Your pressure is about 56 to 60 psi. Again, this is about four bars. You'll get a cetyl/stearyl alcohol ethoxylate. These are used in cosmetics -- very extensively in cosmetic formulations . They're also used in pharmaceutical topical applications. Almost all types of things that are used in facial creams and what-have-you have cetyl/stearyl alcohol or cetyl/stearyl alcohol ethoxylates in them.

This is where you add propylene oxide to it and these are products that are going to pharmaceuticals . They have a moisturizing effect and the PO is reacted slightly different than ethylene oxide. Propylene oxide does not react as high a temperature. It takes much, much longer to react. It's a very slow reaction, 24 hours, about 112 to 114 C and about 34 to 36 pounds per square inch or about two bars. The reason you do this, propylene oxide if subjected to harsher conditions will form a propanol content which has a potential of creating side reactions that are adverse to what you want to produce. So, it's a much slower reaction. Again, your catalyst here is either

sodium hydroxide or potassium hydroxide. You have it under a base condition. The entire thing is under nitrogen atmosphere pressure.

Now I want to talk about going to the nitriles. These are used in pharmaceuticals in small amount. Then we'll go from the nitriles to the amines. This is a very large market area. If you take hydrogenated tallow, fatty acid, ammonia and a catalyst, your time is about eight hours. Your temperature is about 271 C to 282 degrees C. Your pressure is 50 to 60 psi or about four bars. You wind up with a hydrogenated tallow nitrile. This is a first step going to an amine. The nitrile is actually used, to a very small extent, in certain pharmaceuticals .

You take the hydrogenated tallow nitrile, more ammonia, hydrogen and a catalyst, and about three hours at 138 to 143 degrees C, 340 to 550 psi and you will wind up with tallow amine. I do not have a slide, but then you take the tallow amine and you distill it just the same way you distilled the tallow fatty acid, and you get the separated different amines. You get the stearyl amine, oleo amine, and the C16 amines.

Now , this same identical process is used

in inedible tallow when we want to go through this process and take the amine and further derivative it all the way to a fabric softener. This is the exact process that's used. You take it -- if you're going to go to a quaternammonia compound, you would take the particular amine -- you can take tallow amine directly or you can take stearyl amine or allyl amine and you react it with methyl chloride. You take it to a tertiary mean and then you react it with either dimethyl sulphate if you want the sulphate quot, or you react it with methyl chloride again and you'll have the chloride quot. This is how your bactericidal quots are made. Again, the particular one on the methyl chloride reaction is at high temperature and pressure. I'm sorry. I do not have a slide for that, but that's also done under a closed inert atmosphere of nitrogen.

Typical tallow mean distillation is basically the same, about four hours, 274 to 320 degrees C, and you're doing it under vacuum. You do not have a color problem and color deterioration. Now, this morning, there were questions asked on colors and what about the users of tallow and higher temperatures. Color is very critical and renderers know that. We specify any material coming into our

plant. We have contracts. We have specified no head material can come into our plant. That's in a contract with our suppliers. Since we buy the quantity of tallow that we buy, we can dictate how they're going to process it, and they have to certify it.

The safety measures along these lines are going to be covered by Dennis in a later presentation. But one of the measures that the manufacturers and processors of tallow all do is, we specify the conditions of what we want, what we'll buy . If we want certain things left out, that's put in the contract. I assure you that the people who sell to us have no problem complying with those requirements. We do not need the tallow to be discolored because the conditions we're going to operate under far exceed anything the renderer could possibly do. As you've seen here -- this is what I've already presented -- the temperatures and pressures and times and conditions we're operating under far exceed anything in the rendering industry.

You can not make the products unless you do the conditions that I have outlined. They just won't happen. Industry has far exceeded all the conditions, and those were minimum conditions that

we're referencing to back to Dr. Taylor's work. What we want you to do is look at the conditions we operate under and the conditions that products are manufactured under and why they're manufactured that way.

Taking a look -- this is a comparison and it's just a summary average of Dr. Taylor's 20 minutes versus three to four hours, 133 degrees to 248 to 271 C and 48 or 3 bars to 710 to 730 psi. We're operating under much, much higher conditions. Now the question on something going up a distillation tower, what we actually do when we distill tallow, fatty acid, we take it to the gaseous state and recondense it. It actually goes from a liquid to a gas and condenses back to a liquid. You will not get a protein molecule to do that.

Well, I think I'm out of slides, so let me sum up this. I've tried to not give you all the different ways you can make derivatives and I tried to laboriously tell you all the different products. Witco makes -- between blends and actual products -- over 1,000 derivatives and products off of tallow. We're not the biggest in the world, but we're one of the largest. We do not do any rendering. We

purchase our tallow and it is purchased under contract to our specifications. Those specifications, we go -- and Dennis will cover exactly how we maintain those specifications. There's a program set in place that substantiates industry's position, and what we do, and how we do this. Again, it's not uncommon for multinational companies to do partial processing in one plant and ship to another plant. That other plant can very well be in another country. It will very well show an importation in that country, but what really got shipped was not necessarily the way the tariff is set up on it.

I think that I again want to stress the importance. We showed you the time, temperature and pressure. We do our splitting in the temperature in there -- when I say we take the fatty acids to the vapor phase, that we use counter flowing steam to separate the fatty acid from the glycerine. That's high pressure steam and it's counter flowed. It's a continuous operation.

With that, I'm going to end my speech and 1'11 try to answer any questions someone might have.

(Applause.)

CHAIRMAN BROWN: Thank you, Dr. Green.

Committee questions?

Yes, Will?

DR. HUESTON: You just talked about hydrogenation. That takes you from a soft tallow to a hard tallow, correct?

DR. GREEN: Yes, yes.

DR. HUESTON: Now, does saponification begin with hard tallow, or do you start saponification with soft tallow?

DR. GREEN: You can do it either way.

DR. HUESTON: Okay. And transesterification, does that start with hard or soft tallow?

DR. GREEN: Again, you can do it either way there. But as a rule, most large true-put units do some partial hydrogenation. There's a reason for that. It aids in the way you get the processing to go. We do a partial hydrogenation on all tallow in our facilities where we run it through a unit.

DR. HUESTON: One other question, and you touched on it there at the end. All of the tallow that's coming to you has some level of impurities, in other words, some level of protein residual. Now, in this process, what happens to the

protein residual? If you're cracking or splitting and you're vaporizing, then you say that proteins don't vaporize. So, the proteins --

DR. GREEN: You would wind up in a still bottom. You have still bottoms which go out as greases. I don't think I can say it. You can not get a still to go dry. If yOU do, you're going to have a detonation. You've always got a little bit of a still bottom.

CHAIRMAN BROWN: Leon?

MR. FAITEK: Dr., do yOU buy both edible and inedible tallow for your products?

DR. GREEN: We process both edible and inedible, but anything that goes into food or pharmaceuticals is strictly made from edible.

MR. FAITEK: Thank you.

CHAIRMAN BROWN: Other questions?

In the series of slides that you showed, Dr. Green, I got a bit lost in terms of the following question. There were a few processes in which -- I think there were perhaps one or two in which the temperature was under 100 degrees Centigrade.

DR. GREEN: Yes.

CHAIRMAN BROWN: I think you explained

that input material for that had already been exposed to more rigorous conditions.

DR. GREEN: That's correct.

CHAIRMAN BROWN: There were a number of slides in which the pressure was either atmospheric or vacuum. In each of those instances, have the input material been subjected to a step in which higher pressure have been necessary?

DR. GREEN: Yes. One of the areas you're talking about is like in fused calcium stearate. The stearic acid was distilled out of tallow acid and the tallow acid was stilled out of the tallow. so, when you split the tallow, you've been through two high temperatures, high pressures. Under making calcium stearate -- you use calcium hydroxide -- you're under a very alkaline condition.

CHAIRMAN BROWN: Yes, that was my sense but I wanted to be sure that each of the ones that you showed, even when they didn't meet the combination of time, temperature and pressure --

DR. GREEN: Right .

CHAIRMAN BROWN: -- had at least at some point before that input material was processed, undergone a step in which those three criteria were met .

DR. GREEN: Yes, it is. For instance, the calcium stearate is not made in the same plant that we make the tallow fatty acid or the stearic acid. Actually, we manufacture those in one plant and do an interplant transfer. The calcium stearate is actually made in another plant.

CHAIRMAN BROWN: Ray?

DR. ROOS: How much of tallow doesn't go through these further processing and is used, I guess at the hard tallow stage?

DR. GREEN: All of our tallow goes through the processing. We do not make soaps. I gave you saponification, but Witco does not manufacture soaps. All of our hard tallow is processed. In the inedible tallow, most of it is processed into all derivatives. We never stop at a tallow that's sold as tallow. We do sell some inedible tallow fatty acids, but most of it is converted to a means.

CHAIRMAN BROWN: Other questions?

Yes, Dr. Green, you have, I think, pushed the conservatism of this Committee to its limits. About all we could require was that you added a bleach step somewhere along the line. But we'll do our best. Thank you very much, Dr. Green.

(Applause,)

CHAIRMAN BROWN: I think we can go right on to the next presentation, if that's agreeable to the committee, without a break?

This will be a description of the manufacturing process for magnesium stearate by Philip Merrell of the Mallinckrodt Chemical Company.

DR. MERRELL: We have to set up the slide projector here, and aim it.

I'm Phil Merrell from Mallinckrodt where I do research and development on inorganic products. Magnesium stearate, being an inorganic product, is my topic today. I thank Dr. Chiu for recognizing the importance of magnesium stearate in the pharmaceutical industry. It's basically ubiquitous. Every solid dosage form -- virtually every, I don't know about every one -- virtually every size dosage form of product that goes in the pharmaceutical industry using magnesium stearate as a lubricant.

Magnesium stearate is used to the extent of about 1.5 to 2 million pounds a year in the United States for pharmaceutical application. There's other applications, but the ones we're concerned with here are pharmaceutical. It's use per tablet or per solid dosage form, which can be

gel caps or gelatins or tablets, is between about a half a percent to two percent -- generally, between a half percent and one percent. Somebody told me that there were some up around two percent, but that kind of makes it a pretty slick product. They' re used as lubrication agents and mould release agents. It's got the long chain fatty acid, so it's slick and it allows the tablets to release from the mould, or to lubricate them as they go through the system.

Mallinckrodt is the largest supplier and I guess that's why we were invited. I am speaking about the Mallinckrodt process in this discussion here.

I need to reiterate something before we start this. We went through this a minute ago. Dr. Green alluded to the fatty acid splitting process. The product we buy is really refined fatty acid which is a mixture of palmitic and stearic acid with certain specifications. The splitting process which Dr. Green already mentioned, takes 260 degrees C, 720 pounds per square inch, and about three hours to accomplish. That produces glycerin on the one end and the fatty acid on the other. That fatty acid is then further refined -- and this step is backwards here. We'll just leave it like that -- at 260

degrees, 700 pounds per square inch for one-and-a-half to two hours. I say it gives you refined tallow acid which has the correct palmitic to stearic ratio that we need to produce a product consistently the same. There's a USP standard requirement that the product has greater than 90 percent C16 plus C18 in the magnesium stearate. So, it has gone through these two steps prior to our getting the material. We get the material then from the manufacturer. We buy refined tallow acid and go into the magnesium stearate process.

As Dr. Green said, there are two processes. One is fusion which is just simple acid base. You add the tallow acid to the calcium hydroxide or magnesium hydroxide or the zinc hydroxide, or whatever salt you're making. Our process is quite different in that we add -- we saponify first with sodium hydroxide, making a sodium tallowate which is really a mixture of sodium stearate and palmitate. Then we add magnesium sulfate in the second step. Then it's further refined by we dry it, mill it and package it.

In the saponification step, I'm going to talk about time, temperature and pressures also but you'll see -- not pressure, because we're always at

atmospheric pressure, but you'll see that these are not near the extent of what it's already gone through in Dr. Green's plant. We take sodium hydroxide, tallow acid, make the sodium tallowate which is the salt. The conditions are 88 degrees Centigrade, pH is 8.5 to 9.5, and it's stirred and cooked for about an hour. Then the temperature, is lowered to 75 degrees C, again for about an hour. At that point, it is separated from the water, washed -- I'm sorry.

At that point we add the magnesium sulfate to the sodium tallow solution, raise the temperature up to 88 to 90 degrees for an hour. The pH at this time is neutral, essentially. The pH is adjusted up with sodium hydroxide. Then it is diluted with water and held at 170 for about two hours -- I'm sorry, 77 degrees C for about two hours. At this point, it is filtered out and washed. The drying and the milling steps which also see some temperatures but only for seconds, we flash dry it and then mill it all in one big step. Those temperatures are 121 to 160 and they're only at those temperatures for seconds. Then we just package it and that's really the extent to this process.

The tallow acid that we buy has been treated twice by very high temperatures and very high pressures and long times. The process itself does not have all those extreme temperatures. That's it. Thank you.

CHAIRMAN BROWN: Thank you very much.

(Applause.)

CHAIRMAN BROWN: Questions?

Then we'll proceed to the next presentation by Stan Gorak on the manufacturing processes for polysorbates.

MR. GORAK: Thank you and good afternoon. I'd like to thank Dr. Chiu for inviting me to the presentation and to the Committee for allowing me to present the processing conditions associated with the manufacturing of polysorbates.

I show here the structure of polysorbates. Polysorbates are polyoxyethylene sorbitan esters. This is the structure as shown in the USP/NF. The center of the molecule here is basically derived from sorbitol which is anhydrized. The sorbitol is then reacted with the fatty acid, hence my invitation to this meeting. It's then further reacted with ethylene oxide which reacts at active hydroxyl groups.

The polysorbates as listed in the USP/NF include polysorbates 20, 40, 60, and 80. All have 20 moles of ethylene oxide which is added into the molecule. The difference between them being the fatty acid which is used to start, lauric for polysorbate 20, palmitic for 40, stearic/palmitic listed for polysorbate 60, and oleic for polysorbate 80.

Polysorbates are used in a wide variety of applications. They're a pharmaceutical excipient. They're approved as direct and indirect food additives. They are used in cosmetics, industrial applications, as well as agricultural applications. To get to the polysorbate, there's multiple processing steps involved from tallow. We've heard discussions on tallow and fatty acid. What 1'11 address in this presentation is the processing for the sorbitan ester and the polysorbate. The sorbitan ester is an intermediate to polysorbate. It is also sold as a product of its own, and it's also listed in the USP/NF as well as food chemicals codex.

I won't go into the structure of the fatty acids that much. We've seen that addressed already. Laurie acid, predominantly a source from

Coconut, palm kernel and other vegetable kinds of sources to arrive with the fatty acid. Palmitic acid is primarily derived from tallow. There are also some vegetable sources. Stearic acid is also primarily derived from tallow as is oleic with some vegetable sources for both also available. Predominantly, the tallow is used though because of availability and economics. The vegetable sources are used primarily for kosher grade products.

I'll address the sorbitan esters, the structure and processing conditions of them. Sorbitan esters, the first step is the sorbitol undergoes the anhydration to ring closure with elimination of water. This compound is then stearified with the fatty acid to form the sorbitan ester. The reaction is done under atmospheric pressure, The reaction mass sees temperatures at or above 200 degrees Centigrade for a period of about nine to 13 hours, depending on the product that's being made. Of that nine to 13 hours, approximately one to five hours is at or above 250 degrees Centigrade.

Polysorbates, 1'11 address also the structure and process conditions. The polysorbates are formed by taking the sorbitan ester and reacting

it with ethylene oxide. This 3-ring epoxide adding itself to the active hydroxyl groups and forming a polyoxyethylene chain at each of those. The processing conditions for the reaction mass, which also includes a basic catalyst, both reactions, the stearification as well as the oxyethethylation are basic catalyzed. The reaction mass sees a temperature of greater than or equal to 130 degrees Centigrade for six to eight hours. Of that time, it sees greater than or equal to 150 degrees Centigrade at 30 to 45 psig for a period of four to six hours. Again, it's dependent on the kind of product that's being made.

The materials as excipients are made in conformance to GMPs. One of the presentations earlier showed the big vat with the man stirring the vat to make soap. Obviously, all the processes we've been discussing today are carried out in closed systems and under good GMP and conditions and clean systems. The products themselves that are manufactured are tested, including testing conformance to USP/NF and/or food chemicals codex requirements. The materials we purchase in the fatty acids are all certified to us by the suppliers and we, to our customers, are required to supply

certificates of analysis on the quality of our material. We're subject to internal and external audits . External audits, both by our customers which tend to be very critical and grueling, having their very specific requirements, and we're also subject to FDA audit.

So, to summarize, the fatty acids that we use as our starting material have already been processed at elevated temperatures and pressures that we've already seen earlier in the presentations . The intermediate sorbitan esters and the polysorbates are manufactured at temperatures which at times exceed 250 degrees Centigrade, or see pressures of 30 to 45 psig at elevated temperatures for extended periods. Also, we do use bleach in one of the steps. There was a comment earlier about had everything but bleach. We've thrown bleach in. Also, ethylene oxide is a key reactant to making the polysorbate molecule and it's a well recognized known sterilant.

That concludes what I wanted to present. If the Chair -- open it to questions.

CHAIRMAN BROWN: Thank you.

So, you put in some bleach? Why ? Ethylene oxide doesn't do a thing to these agents.

DR. MERRELL: To a priori?

CHAIRMAN BROWN: Well, we have to say something.

Are there questions now? Because I think the following two and final presentations of the day would go well together as they have a more general orientation. If there are any specific questions, either of Dr. Gorak or any of the previous detailed presentations, let's have them now.

Well, this gives me an opportunity to ask finally if there is any burning question that anyone in the audience might have for the previous speakers?

Very well. We shall have a break and in 15 minutes be back. It is now 2:12. Let's make it 2:30.

(Whereupon, off the record at 2:07 p.m., until 2:28 p.m.)

CHAIRMAN BROWN: On this home stretch of today's meeting, we have presentations by Dennis Walker and Fred Bader. We're negotiating to see whether or not Doug Anderson, who was scheduled to give a very brief presentation tomorrow might finish --

PARTICIPANT: He's not here.

CHAIRMAN BROWN: Then we shall finish the day out with Dennis Walker and Fred Bader.

I introduce now Dennis Walker, Professional Regulatory Services, the Chemical Division, Proctor & Gamble Company, who will talk about oleochemical safety in the United States.

MR. WALKER: Thank you, Dr. Brown.

Good afternoon. My name is Dennis Walker. I'm with Proctor & Gamble Company and I'm representing the Soap and Detergent Association. My intention this afternoon is to build just a bit on Dr. Green's comments from earlier this afternoon, with a focus on the safety of tallow derivatives in the United States. Particular attention or emphasis is going to be placed on several quality assurance aspects.

First, I would like to speak to quality assurance measures to enhance tallow safety with respect to protein inclusion. The decision to perform additional pre-treatment steps on tallow by the oleochemical or the soap manufacturers is largely dependent on three factors. Those factors are the quality or grade of the purchase feedstock that they initially purchase, the oleochemical

process to which they would feed it in, and thirdly, the intended application to which it would be made in. As an example, it is not uncommon for edible tallow, which is a *very* high quality if not the highest grade of tallow, to be used in soap manufacture. Or if not edible grade, then generally the highest grades of inedible tallow are used in toilet soap manufacture. In addition, there are going to be additional pre-treatment steps that are also performed on these tallow feedstocks in preparation for their use in oleochemical operations, or in soap manufacture.

Specifically in terms of the key quality measures of tallow -- and these were covered earlier so I'm going to be very brief on this. But in terms of their use in the oleochemical industry and in soap manufacture, the key measures or quality aspects include the raw color; the refined and bleached color which really represents the best color improvement that can be expected to be achieved for a specific grade of tallow; free fatty acid content which really gives a measure of the amount of decomposition that may have occurred in the triglyceride; the moisture incital impurities in unsaponifiable manner known as MIU. Within this

particular quality measure, the incital impurities measures traces of proteinaceous solids that remained in the tallow,

Typical tallow pre-treatment steps include water washing which can be followed, or is followed by settling or centrifugation. In this particular step where you have the water washing, this results in hydration of proteinaceous material which gives swelling and increased density to this proteinaceous material providing for easier separation. Additionally, other types of pre-treatment steps that are utilized within the industry include filtration -- and this is using various types of diatomaceous earth or other types of clay. Or related to that would be bleaching using what are called bleaching clays. These have been acid activated to remove color bodies. Those are the most common techniques that are used in pre-treatment of tallow. There are other types of pre-treatment including chemical bleaching, also exposure to phosphoric acid. Those are not generally practiced in the United States, but those also are pre-treatment steps that can be utilized with cleaning up or upgrading tallow feedstocks.

One aspect that I wanted to mention is

that as was mentioned earlier by Dr. Green, distillation steps are typical of most oleochemical processes and they remove high molecular weight proteins and also protein degradation products.

To summarize, tallow can be used as purchased, or after pre-treatment, or a combination of both. High grades of tallow are used in toilet soap manufacture. Within the oleochemical industry such as manufacture of fatty acids or other types of oleochemical products, there is more flexibility that could be utilized in terms of the quality of the tallow feedstocks, but these operations involve multiple processing steps including distillation processes that remove traces of proteinaceous material or their degradation products.

On a more general nature in terms of quality assurance within the oleochemical industry, as again we mentioned earlier, the oleochemical industry operates under computerized process control. This includes continuous monitoring of processed conditions. Examples include temperature, pressure, time, flow, among other process variables.

Additionally, the oleochemical industry involves multiple transformation and purification steps. As part of this, it includes routine in-

process testing. Key to this is measures of reaction completeness and additionally, various purity tests are also conducted as part of the in-process testing. One of the predominant techniques that is used within the oleochemical industry, both for purity testing as a measure of reaction completeness, and also in terms of minor component or impurity tests is the use of gas chromatography. That is really a standard within the industry for many of the products.

Also, in terms of oleochemicals that are intended for pharmaceutical, cosmetic or food use, this requires adherence to the food, drug and cosmetic regulations.

Let me back up here just a second here. I have one slide that I want to mention and that was around finished product testing. Again, for products that are intended for pharmaceutical, cosmetic or food use, these are tested against compendia specifications such as the United States Pharmacopoeia or National Formulary Requirements, Food Chemical Codex, and then there's also other types of industry specifications in trade association specifications such as CTFA that are conducted for finished product testing.

Now , as I was mentioning, within the oleochemicals industry, for those products that are intended for pharmaceutical, cosmetic or food use, this requires adherence to the Food, Drug, and Cosmetic Regulations, and also are made in compliance with Good Manufacturing Practice Regulations, GMPs. These are legally binding regulations. They require systems of quality control and assurance, require control of incoming raw materials, require a validation of methods and processes, as well as documentation and personnel training among other requirements. And again, products that are made for these regulated areas must meet the compendia requirements.

There are, in addition, other external quality control factors. This includes internal compliance audits that are conducted widely within the oleochemical industry. In addition, external compliance audits, again, conducted by either customers or by FDA inspectors. Thirdly, within about the last five to seven years, 1S0 9000 certification has become very prevalent within the manufacturing industry, including the oleochemical industry. This is a set of quality management practices that has been established internationally.

It originated out of Europe, but has been utilized around the world. And SO, many of the oleochemical manufacturers have ISO 9000 certification as well.

I was asked to speak briefly on research results indicating that tallow is not a source of BSE infectivity. This has really been covered in detail earlier today, so I will not spend a lot of time on this. It really is based on the epidemiological studies by Wilesmith that were mentioned earlier by Dr. David Taylor, as well as his work as published in 1995 and 1997. I'm not aware of any other work that has been done specific to tallow. I think this has been borne out in other reviews as well, such as the Scientific Steering Committee in Europe.

In terms of the comparison between the US situation versus Europe -- and I've got just a very brief comparison here. What I wanted to show is that in the US in terms of the sourcing, tallow sourcing, and based on the results from our SDA survey, the tallow sourcing is strictly from North America. We do have a couple of survey results that came back indicating use of tallow from Canada that was for subsidiaries of US operations that were based in Canada. Likewise, we had a company who has

subsidiary operations down in Mexico who utilizes Mexican tallow as well because they are located in Mexico. But for those manufacturers that are located strictly within the US, the sourcing material is strictly US tallow.

In Europe, the tallow sourcing is a combination of European-sourced material as well as third country importation. Largely, this is tallow that comes from the US as well as other countries, such as Australia, or perhaps New Zealand, possibly Latin America. But primarily, it's US tallow that is imported into Europe to make up for the shortfall of availability of tallow in the EU.

In terms of the processes, the types of oleochemical processes that are practiced in the US and in Europe are the same. In terms of the process conditions between the US and Europe, they're very similar process conditions. There may be some slight variation as you would expect in terms of operating conditions, but largely, they are, again, very similar because of the fact that the processes that are utilized are also very similar to one another.

To summarize, in terms of the safety of US tallow derived oleochemicals, we have no cases of

BSE that have been reported in the US. The tallow feedstocks are domestically sourced, are processed at high temperatures, under pressure, for appropriate periods of time, include multiple processing steps including purification or distillation steps after cleavage of the tallow molecule. Also, we have various auditing practices in place, internal/external compliance audits, to assure that these types of operations are being adhered to. In addition, you have US regulatory barriers against BSE that are in place, USDA surveillance of animal health developments, both domestically and internationally, as well as continued industry and government monitoring of BSE developments.

One additional point that I wanted to mention and that is the recent opinion by the European Union's Scientific Steering Committee. Again, this was mentioned earlier today, but in this particular opinion that was adopted on March 26th and 27th of 1998, they adopted the opinion that tallow derivatives are considered safe provided the raw material is fit for human or animal consumption, or provided -- regardless of the source -- production processes use appropriate, validated and

scientifically up-to-date inactivation methods.

They cite two specific sets of criteria, again, which were covered earlier today. This includes the Scientific Committee of Cosmetology opinion fOr cosmetic products and the CPMP opinion for medicinal products. As was covered before, this includes hydrolysis or transesterification at 200 degrees c, 40 bar for 20 minutes for glycerol, fatty acids, and esters, or saponification with 12 molar sodium hydroxide in the batch process at 95 degrees C for three hours and the continuous process at 140 degrees C, two bars for eight minutes or equivalent. In the European EMEA or CPMP, conditions are very similar. The only difference is that they cite, in terms of hydrolysis or transesterification, under pressure as opposed to a specific 40 bar pressure.

so, in conclusion, US oleochemicals derived from tallow, in our estimation, present no discernible risk of BSE infectivity for the reasons cited: tallow feedstocks of domestic origin, harsh operating conditions, no case of BSE diagnosed in the US, government protection and regulatory surveillance in place.

Thank you.

(Applause.)

CHAIRMAN BROWN: Thank you, Dr. Walker.

Dr. Bader. The last time we heard from Dr. Bader was the last time this Committee met. Among the things he showed was a rather intriguing slide giving the mathematical modeling risk of eating a hamburger in London in the context of being run over by a car or developing diabetes. I wonder if he has a similarly intriguing mathematical model for us today?

DR. BADER: Actually, I have not presented to this group before. That was a different meeting.

CHAIRMAN BROWN: Oh.

DR. BADER: But I do have that slide to present.

CHAIRMAN BROWN: Good .

DR. BADER: I would like to thank Dr. Brown for the invitation to be here.

I am Fred Bader. I'm vice president of worldwide operations for Senecor, Incorporated. I'm here today speaking on behalf of the Pharmaceutical Research and Manufacturers Association of America, also known as PhRMA. We're going to be talking about the safety of pharmaceuticals.

In her introduction, Ms. Holston

discussed the complexity of the process of evaluating the safety of products with respect to BSE. That is very much a challenging task to try to deal with. She also mentioned the law passed in Europe last July which, if it had been allowed to go into effect, would have pulled roughly 85 percent of the pharmaceutical products in Europe off the market as of January of this year. Fortunately, they delayed that decision. They're still trying to wrestle with it. It's difficult for us to anticipate what the actual impact of that kind of a move would have been, but it's hard to believe that it would not have been devastating to the European health care system and would have had impact on the US system as well because some of the products we consumers use are produced in Europe.

We'll talk to the next slide and it will show up someplace. One of the concerns that PhRMA has is that we develop pharmaceutical products on the basis of benefit to risk. Benefit to risk is the basis of development of products. It's a basis of approval of products in the United States. It's generally the basis of use of products by physicians and patients and we think it's the proper way that things should be done. A pharmaceutical company

will spend 10 to 15 years and roughly half-a-billion dollars today developing a pharmaceutical product. We go through many, many dry wells trying to come up with products that can really treat some of the new diseases that we face.

Pharmaceutical products should continue to be approved and prescribed on the basis of benefit to risk. One of the real concerns with the situation that occurred in Europe is, there was a chance of having a wholesale-wide group of products suddenly pulled off the market without any analysis of what the impact would be. That, actually, was quite frightening to many of us in the industry. We also appreciate that this also had an effect on many people in FDA and other parts of the government -- USDA and many of these people helped to get the Europeans to rethink this particular situation.

If we talk about benefit to risk, one of the things for us is to also develop some idea of what is the risk of BSE and pharmaceutical products. so, since 1992, we have been working on trying to come up with ways of assessing what the risk of BSE would be in products. We need to define the BSE risk and that's the basic problem. The public in general wants to know whether something is safe or

unsafe. The reality of life is, life is not that black and white. Only answers talking about relative risk can be credible because nothing is absolutely one extreme or the other. A true zero risk never exists. With BSE, there's a tremendous range of risk. So, some risks could be quite high, some risks can be extremely small. We have to get our arms around those different levels of risk.

There's also a problem that at many of the risk levels that we're dealing with, there is no data. There's really no cause and effect data in existence today for human infections with BSE. There are roughly 24 cases in Europe where people have come down with new variant CJD, but there's so many different bovine sources and potential causes that, as I understand it, no one has been able to attribute any particular cause to these particular patients. It's very likely that we will never have -- or hopefully, we'll never have the statistical database to be able to do that.

In the pharmaceutical industry, we can look at BSE as an adventitious agent. An adventitious agent in pharmaceuticals would be an undesirable organism, infectious agent of one kind or another. Mycoplasma, virus, bacteria are the

ones that we usually deal with which, through one means or another, can get into a pharmaceutical product through raw materials, through contamination, through operators or different types of things that can happen. We believe BSE can be treated as an adventitious agent and pharmaceutical companies have quite a bit of experience dealing with and defining the risks of adventitious agents which is one of the reasons why we undertook this particular task. We need to develop some guidelines.

We have a long history of making safe products, safe and adventitious agents as a whole, and there are also a large number of defined and accepted limits for these agents. Some of these are in federal laws. Some of them are in guidelines from the regulatory agencies. Some have been set by standard setting bodies like US Pharmacopoeia. Others are just standard industry practices that the industry as a whole generally follow. The difficulty we have today is we have no standard practices for limits for BSE.

When trying to assess risk, there are a number of major risk factors that have to go into any kind of calculation that one might make. I put

up some of the major ones here. The key things are the fraction of animals that you would be obtaining that might be contaminated. That generally right now can be based on a number of things. For commodity products like the tallows and gelatins, et cetera, generally, this is mostly determined by geographical origin of the animals. The number of animals you use per batch obviously increases the risk that a batch could be contaminated. The particular tissues that you're using and their infectivity have an impact. Reduction of infectivity by processing which you've heard quite a bit of discussion on, the tallow derivatives today and some of the severe conditions that they're exposed to, and how that might may reduce the infectivity. There are questions of species-to-species barrier -- what is the barrier between going between from bovine to human? And then -- administration of products, oral products for example, generally require a much higher dose than a product that might be directly injected.

The difficulty with this whole area is that for each of these items, there's a fairly wide range of debate. We do not have a lot of good actual numbers. In some places, the numbers are

better than others and others in certain areas, they're fairly speculative. Now, we're trying to come up with better ideas for these. Some of these things actually will be the product of the FDA workshop that's being held in June where a number of these factors will be directly looked at. Again, what we need to do is have some of the top leaders in the world continue to work and try and define these better so we can have the best numbers possible.

What's much easier to define generally is the results that one wants from a risk assessment. Typically, one that is commonly asked, were such things as the risk that a batch of product might be contaminated? The potential number of infections that might exist in a batch if it were contaminated? At the user level, the physician and patient level, the concern would be the risk of infection per dose or per treatment. A treatment would be a number of doses to successfully treat a disease, however many doses that might be. If one looks at a more global level, one also has to be concerned about the risk of infections per population.

Now, I would strongly emphasize --

because I will show the slide that Dr. Brown introduced which does give some idea of estimates of numbers . But we have to be very careful in looking at these things that at this point in time, there's an awful lot of uncertainty. So, we're basically making the best estimates that we feel we can make at the present time. One of the reasons to do this is to create a model that forms a baseline estimate from which we can make adjustments and changes as new information is gathered. To a certain extent, this also helps to direct us in trying to determine what information is really needed, what kind of research might need to be done to successfully get the information that we'd like to have.

One of the more difficult things to deal with when looking at these risk assessments is trying to understand what the numbers mean. For example, if I said that there was a 2.5 times 10^{-8} risk per dose, it's fairly difficult for most of us to understand what exactly that means because we don't normally deal with numbers like 10^{-8}. Even those of us who work with numbers a lot, come from the scientific or mathematical backgrounds, have a hard time conceptualizing what this means.

But there are different ways that we can

convert this into things that may or may not be more meaningful to you. For example, that kind of a risk per dose would mean that we would expect to see roughly 2,5 infections per 100 million doses. It also means, another way of saying the same thing is one infection per 40 million doses. Another way of looking at it is to say that if a patient took 40 doses in a treatment that the patient would have a risk of roughly one per million of becoming infected. Another way of looking at it would be to say if a pharmaceutical company, for example, sold a million doses per year, we would expect to see one infection in 40 years. So, there's lots of different ways to express this. Some may have more meaning to one person than another.

Another thing that we have to do is to try to put risks in the context of the risks that we face every day. Most of us don't think about these things an awful lot, so we put together some -- these are basically data that comes from US statistics. For example, roughly two people per 1,000 each year will die from tobacco related causes . If you look at things like alcohol related, motor vehicle accidents and AIDS, you're talking numbers of a few per 10,000 per year will die from

these types of sources. Food poisoning is roughly four per 100,000. Bicycle accidents, again, roughly four per million. Every one of us -- I can remember the day that I bought each one of my three children a new bicycle and of course, never thought that we were exposing them to this kind of risk. Although they usually came back soon after with skinned knees and ankles, and elbows, and whatever. When you think about something like lightning and tornadoes which is kind of a sporadic but low probability risk, or something like dying from a bee or wasp thing, these are numbers that tend to range in a few per 10 million range.

Now, we can plot these types of numbers on a risk chart. If you look at the right-hand side of the chart over here, this would be highest risk and this would be 10^{-0} risk which is basically one, or a one to one risk, 100 percent risk at this point. As you move to the left on the chart, you're moving to lower risk. 10^{-6} would be one per million. 10^{-9} in here would be one per billion. 10^{-12} would be one per trillion, and beyond that I forgot what the rest of the numbers would mean, but you get the general idea. The area that is shown in red basically describes this area, the kinds of

numbers that I was just giving, typical common causes of accidents or deaths in the United States today. You can see all of these run in a range of roughly one in 100, to say, one in 10 million.

If you looked at a risk that would create one death per year in the United States, that would fall in this range. It would be one in 250 million, roughly. A few things we may want to say -- this data here all comes from actual data, from statistical data that's collected. There are always accuracy issues with this. Not every death is properly reported. Different causes can be wrong. But on the other hand, you can look at this sort of thing, and these kind of numbers are probably within plus or minus 25 percent, 50 percent, something like that. They're going to be fairly close. But this is experimental or directly collected data.

We've put a bar up here which 1'11 talk about on the next slide, talking about something that might be defined as insignificant risk. We know that a true zero risk does not exist, so we can't tell anyone that something is perfectly safe. On the other hand, we can define a risk that's low enough that we would deem it to be so insignificant that it's not worth worrying about or taking action

on. Now the question is, what kind of risk -- what level do you reach that risk at? There are different things that have been proposed at different times. For example, some people have claimed that if the risk of getting new variant CJD from contamination of BSE, if it's not greater than the risk of spreading CJD, which is one in a million, that that would be acceptable.

The one problem I would have with that is that would mean we'd accept 250 cases of new variant CJD per year in the United States. I think from an epidemiological standpoint of what that could do with its potential to spread, that would probably be unacceptable. We could set a limit of less than one person in the United States per year and that's a fairly reasonable limit to set. On the other hand, with bovine products, we have to be careful because there's many sources of products. so, if you say that for one particular product -- which there is a lot of different kinds of bovine products out there -- you could accumulate a number of these and come up with something that starts to really become a detectable level of risk. What we have proposed as a round number is roughly one in 10^{10} or one in 10 billion which is basically forty-

fold lower risk than one per year in the United States .

Now , this is the slide that Dr. Brown mentioned earlier. We have used some of our analyses to look at a number of different pharmaceutical excipients which are commonly used in a lot of pharmaceutical products. At the lower end here, we see magnesium stearate which -- this is a three milligram dose based on US material. The stars here would actually denote the exact number that we came up, But there's something we have to be very careful about here. When you're doing risk assessment and doing models with numbers which are estimates to start with, it's dangerous to grab hold of a single number and hold on to it as if it has a lot of meaning. So, it's more important to look at this chart from the standpoint of what region of the chart we're sitting in and look at it a little bit more globally from that standpoint. This is magnesium stearate. This is lactose which is a common filler that's used in making some pharmaceutical tablets and capsules.

This would be gelatin. I'll explain with gelatin. We've looked at four different cases here. There's cases one, two, three and four.

There's two European cases. The higher risk case would be the case where the head and spinal cord is removed but the vertebrae or the spinal column is still used. The case here would be the case where European material is used where the head, the spinal cord, and the spinal column is removed. There's two cases shown here for the United States. Again, the first one would be similar to the first one for Europe. Again, int his case, there would be no head, no spinal cord, which is typically the case for bone going into gelatin, but the spinal column would be included. Then the second case would be a case if we forced the removal of spinal column from the bone or gelatin process. Now , this also gives a good example. Some -- the assumptions that you get, we're looking at a range here of a number of orders of magnitude. Again, depending on sourcing and exact products, we've seen some of these ranges could be fairly broad. All of these particular cases, all three cases show up as basically falling in this insignificant risk region.

One other point I would make with the insignificant risk region. We talked about data over here as data which we can actually -- there's actual numbers and statistics on that we can

actually do measurements on. When you run into risks that run out in this type of a region, if we replace one product with another one because we think it's going to be safer, the question is how can we prove that that other product is actually safer when we're running in a range here where it's not possible to get measurable data. So, the only way we can do that would be with some other -- basically comparing two different models of things or whatever. We have to be careful not to get to the point where we may want to replace one thing which is fairly safe with something else which we think is safer, but may actually turn out that it may actually somewhere along the line cause problems that would be in a much higher risk area.

Now, the other cases on here -- in order to try to look at cases which would be particularly higher risk, we did some comparisons in some of this just to get an idea of what the model might predict under certain circumstances. We looked at, for example, BSE from US hamburger compared to BSE from UK hamburger based on 1990 for UK which would have been probably the number of potentially infected animals that were available in England at the time. If you look at the two, the US hamburger is a very

low risk, This is based on quarter pound hamburgers. With this number per burger, if the average American ate 100 quarter pound hamburgers per year and everyone did that, we would expect to see one case in the United States in 400 years. So, this gives you an idea of the level of safety that this has.

Now, when you look at the UK case, this risk is at a point where with the numbers here, if every UK citizens ate 100 quarter pound hamburgers per year, we would expect to see roughly five cases per year in the UK. So, that's clearly in a region where we start to move away from insignificant risk and we have to start being a little bit more concerned. Now, based upon this, UK did take a number of actions to try to protect their beef supply which would have significantly lowered this risk and pushed it farther out.

Now the next case of comparison actually is this ovoid here which is eating a dish of adult cow brains in the United States compared to eating the same dish of adult cow brains in the UK in 1990. What you'll see is, this basically has to do with the relative risk of BSE being in animals at the two countries at the time. In the UK, this is roughly

one in a 100 risk, a fairly high risk. It's something I guess I would not have done back in those days, but I don't eat cow brains anyway. Some people do. In the US, it's a risk that, you know, is roughly one in a million. It's no more dangerous than riding a bicycle, I suppose or, you-know, actually, food poisoning. Dying from food poison is an order of magnitude higher. So, you can make a choice on whether you want to take that risk or not.

The one other case that's on here is one -- this does not have to do with BSE, but one case where we do have data. This is the infection of people with CJD from the categoric derived pituitary human growth or growth hormone that was used in the '60s to mid-' 70s, where this was basically transmitting CJD from cadavers to patients being treated. Basically, this ran in a number per thousand of people treated. We ran the model. We came up with numbers that were fairly similar to this which is nice to see. Also, we have to be careful. That's not a validation of the model. If we had a substantially different number, it would have been invalidation of the model but that one test does not validate the model by no means, especially since it's CJD. So, a lot of the BSE

part of the model is not being used here. Now, this is a good case though that this problem was recognized and the categoric product was replaced by recombinant human growth hormone in the late '70s. Then this product that caused this problem hasn't been used for, what, over 20 years, I believe.

Now, if I haven't already saturated you, this is also looking at fatal disease. This is the United States again. This is 1994, US National Center for Health Statistics. Again, to put all of these in context, roughly one in a 100 Americans will die, you know, this year. This is 8.8 per thousand, but it's roughly one in a hundred. That makes sense because our life expectancy is less than 100 years. So, that seems to come out all right. If you look at major cardiovascular disease, roughly four per thousand will die from cardiovascular disease; cancers and malignancies, two per 1,000. We get into things like tuberculosis, a much rarer disease but still six per million. So, this gives us an idea of the relative risks that we have from dying from one disease or another.

Now, when you talk risk to benefit, if you're talking about someone who already has cardiovascular disease, this risk is much higher

than the numbers that would be shown here. Of course from a pharmaceutical standpoint, there are products on the market that often can help relieve symptoms of disease and extend people's lives. In this day and age, many of us my age are already taking our aspirin a day and perhaps a cholesterol lowering drug of one kind or another, getting exercise to try to keep in shape, et cetera.

So, this is just to summarize that we do believe that as a pharmaceutical industry, we need to try to come up with estimates of what the risks are in pharmaceutical products. To date, most of the things that we have looked at have come out relatively low. It's not terribly surprising because pharmaceutical products are used in very small quantities, generally. Typically, we show data on the tallow derivatives, gelatin and lactose, and they appear, at least in our analysis to be in the insignificant range. We certainly would encourage the TSE Advisory Committee, the FDA and any other bodies that would be involved that in looking at pharmaceutical products, we would hope that these would be looked at as a one-on-one basis to evaluate the benefit to risk and not wholesale removal of products, you know, from the market.

(Applause.)

CHAIRMAN BROWN, Thank you very much, Dr. Bader.

That concludes the presentations on Day 1. The Committee's major work won't begin until tomorrow. This has been an education. But we do have time now for anyone on the Committee to ask anyone who has presented anything today a question.

Leon ?

MR. FAITEK: I talked to you during the break regarding my question. Perhaps in response to that question I had, maybe I could ask Mr. Mitchell Kilanowski to come up and answer the question that he answered for me, and that's regarding the use of brain and spinal cord in tallows.

MR. KILANOWSKI: Well, as I said, as I understand it from the major packers that the heads and the spinal cords are not used in edible tallow.

CHAIRMAN BROWN: Okay.

DR, LURIE: Has anybody done any kind of formal survey of that question?

MR. KILANOWSKI: No. I've surveyed two of the major packers and we ourselves -- we're edible tallow manufacturers also -- and we do not include spinal cords or heads. That probably

represents, I'd probably say, 70 to 75 percent of the industry. I'm reasonably confident that the other ones aren't either because pressure has been put on them not to include it.

DR. FRANCO: And there is a reason for that, Paul. I could help Mitch.

Four percent of the processing plants processing cattle in the United States produce 80 percent of the production. Those are the biggies, the Montfords, the Excells, and the big processing plants. Those people concurrently do render it. That's where you get your rendering material from, from your big processing plants. That is the reason why Mitch probably alluded because those big processors that do edible also take the necessary precaution to help retain the markets.

The problem with some of the small processing houses that supply the independent renderers will differ considerably, depending on the inherent policy of the small slaughterhouses. But for the big renderers, I think that's a pretty accurate statement.

CHAIRMAN BROWN: Thank you.

DR. OLANDER: One more question on that theme. The vertebral column is removed or the

spinal cord?

MR. KILANOWSKI: The spinal cord as far as I know.

DR. OLANDER: Okay, thank you.

CHAIRMAN BROWN: Just to reemphasize what we are about and going to do tomorrow, I'd like the Committee again to sift through what has been presented today in terms of the questions that we're going to be asked to answer. I'm not going to read them all again, but basically, we're being asked two questions. One has to do with tallow and one has to do with tallow derivatives. I think from today's proceedings, you can see why the FDA elected to separate these two questions into two.

The questions are: does the available scientific information justify a change in the current FDA guidelines that bovine source materials for the rendering of tallow should not come from BSE countries as designated by the USDA. The same question is asked in the same manner for tallow derivatives . Then if the answer to either one of those is yes, then we're going to be forced to justify that response. Actually, we should be asked to justify either response. But if we decide that the FDA position is tenable and should be continued,

that's the end of it . If we decide that we'd like to make a recommendation that the FDA change, then we have a number of ways in which we can move.

So, again, we learned an awful lot today about the industry, about the product, about the processing, The bottom line is, we are going to be asked to advise the FDA on whether what we have learned today and what we know apart from that is how it plays into whether or not the FDA should be changing its stipulations about tallow or tallow derivatives . We're going to be asked those questions separately.

With that in mind, does anyone have any additional questions that they might like to ask anybody today?

DR. SCHONBERGER: I was wondering if Fred Bader could expand a little bit on the chart that he gave which put tallow derivatives in the insignificant range? And whether he has, also, a similar type of assessment for tallow since that's what the Committee is supposed to evaluate?

CHAIRMAN BROWN: Yes, maybe that's a good idea. This is a mathematical model.

Fred, why don't you tell us all of the assumptions that went into that number? And then **as**

Larry said, if you would also add -- it was derivatives . If there's any number for tallow as such . In other words, add two subcategories.

DR. BADER: I have never run the numbers on tallow directly. Tallow isn't used directly as a pharmaceutical excipient or product, so there's never been a reason to run that. There may be other people here who have done that. The tallow derivatives, magnesium stearate in particular, US sourcing, we would assume one in a million animals could have BSE, though we're a BSE free country.

CHAIRMAN BROWN: so, that's the first assumption --

DR. BADER: That 's the first assumption.

CHAIRMAN BROWN: -- which is that it may be one in a million cattle in the US might have undetected BSE.

DR. BADER: And that's basically, I believe, the limit of detection of the current USDA program to, you know, look for infected animals, et cetera, so that there's always a limit of detection which you discussed when you do these dilution experiments. There's some point you can't get below. That's why we use that particular number.

Some of the numbers that we use are

process industry numbers of how much material you get frOm each animal, et cetera, which come from the industry input. From a reduction by processing, we use an eight log reduction for magnesium stearate. We would judge that as a very conservative number. But generally when we do assessments of adventitious agent removal --

CHAIRMAN BROWN: Yes, where did that come from, eight log reduction?

DR. BADER: Basically, it would be the -- if you ran the experiments, that would be the limit you would be able to detect. That's why we've used that. No one has run those experiments. On the other hand, no one has ever felt it was necessary to run the experiments.

CHAIRMAN BROWN: So, I'm getting the sense that most of your assumptions are based on the limit of detectability. Since nothing is detectable, that's the upper limit of your assumption, pretty much?

DR. BADER: That would be the limit. If yOU looked at, you know, David Taylor's work, or you're looking at perhaps a three or four log reduction at 135 degrees C under pressure for 30 minutes, and if you did the standard chemist

calculation of doubling the rate every ten degrees, you would come up with somewhere around 500 logs or 600 logs reduction or something in that range.

SO, I mean, if you take that kind of linear extrapolation -- again, typically, when we look at adventitious agent removal these days, you can't make those extrapolations. So, you take what you would be able to see as a limit. But again, to date, I'm not sure that anyone has ever looked at trying to run those experiments. Most people have felt the experiments to run because tallow is such a severe condition, it wouldn't be worth actually doing assessment of -- date logs as numbered.

Other numbers in there we used were oral dosing that 100,000 intercranial LD-50 units would give a single oral dosing unit. Again, those are fairly standard literature numbers that have been used. In looking, actually, in that particular number, we took a worst case scenario and we assumed that heads and spinal cords were going in the tallow. My understanding from my own experience with meat packers, et cetera, is that the heads and spinal cord do not go into edible tallow. They go elsewhere. Again, that was a worst case assumption, so that adds quite a bit to the numbers. The

infectivity of bovine brain that we're using is around 10^{7} per gram based upon bovine-bovine rather than bovine-mouse. Again, you're well aware of how those estimates come about. We're using a bovine to human species barrier of -- basically, we're assuming that the bovine to human species barrier is the same as a bovine to mouse. So, those are the basic assumptions that go into that.

CHAIRMAN BROWN: So, you know, these are really fun mathematical games so far, said without criticism because I love them. But if you changed one assumption by two logs and another assumption by one log, to give an example, I'm not sure that the 100,000 IC doses or 100,000 oral doses make one IC dose is in fact what everyone here would agree is the proper number.

So, you might go in one direction in one assumption, and another direction in another. But you'd be hard pressed to take a risk of 10^{-20} and bring it up to 10^{-9}. I mean, you might get two or three orders of magnitude at the most, which would still keep it way down at the end of the scale.

DR. BADER: Well, and the other thing, when you look at a model like this, if we're that far off in this risk assessment so that tallow

derivatives, for example, magnesium stearate is that dangerous, then you'd have to look at all the other impact on society from that same set of assumptions because it would say that everything else that's to the right of the curve for magnesium stearate is also that much more dangerous. I think there's no data to really support that. So, you have to look at the model also as sort of how it fits as a total.

CHAIRMAN BROWN: Yes. I don't think I agree with respect to a right shift systematic. I think it depends on the assumptions you've made for each individual --

DR. BADER: That's correct.

CHAIRMAN BROWN: -- one which are going to be different for each one.

DR. BADER: Some assumptions are constant and some are different for each one.

CHAIRMAN BROWN: Yes, yes.

DR. BADER: That's right. So, it depends which assumptions you change.

CHAIRMAN BROWN: Yes?

DR. LURIE: You sort of urged us to consider all of this in the realm of benefit to risk. But really, the data that you show us are really about risk.

DR. BADER : Right.

DR , LURIE : It seems to me that the question here is -- and you asked us, in effect, to dismiss the risk from these products as insignificant, compared to other risks that we are familiar with in some sense accept. I guess I have two comments on that and wonder how you would react to them.

The first is, the list of risks that you present are indeed things that are either in some ways irreducible like tornadoes, lightening or are things that we are, in fact, doing something to try to reduce the risk of. So, I think that's one part of this. The real question, it seems to me, is not if the risk is insignificant, but whether or not the risk can be further reduced without any adverse effects, by which I mean a shortage of product for the production of pharmaceuticals in this country -- from which I don't think there is -- or any other, you know, effects upon the industry. So, the question is, can we reduce the risk at no cost to us globally, you know, in the society that is?

DR. BADER: I would certainly totally agree with that. One of the reasons to look at these systems in the first place was to try to

determine where do we have significant risk? What kind of things should we be looking at?

I would say that most pharmaceutical manufacturers today are evaluating sources of other materials, trying to get a better sense of what the sense might be. If there are alternatives that are available, that may be well looked at. Although you have to be careful not to jump from something that has a long history of safe use and move to something you know very little about which may actually have a higher risk. so, that's a balance that one has to be careful to watch.

DR. LURIE: But really, we're talking about a pharmaceutical made from tallow derivatives from Europe versus a pharmaceutical made from cow derivatives from the United States, right? I mean there's no intrinsic reason to think that one would be any more effective or less effective than the other, I don't think.

DR. BADER: I think both are equally available, and so there wouldn't be. There are cases -- gelatin for example is a different case because most of the capsule gelatin that's used in the pharmaceutical industry does come from Europe and there's not the capacity here for that. So,

yes, again, most pharmaceutical companies would be sourcing away from Europe for just about everything they can source away from Europe at the present time.

CHAIRMAN BROWN: Leon?

MR. FAITEK: Dr. Taylor's study seems to be very pivotal in this whole discussion. If Dr. Taylor is here, I'd like to ask him in his charts where he used different temperatures and different pressures and found yes, no infectivity.

What basis did you use to say that there was no infectivity? Is there any quantitative measurement where you said yes and no?

DR. TAYLOR: Right . Just to set the record straight to start things off, the list of procedures which I showed, of that list only one of the group of the three at the bottom was, in fact, carried out using steam under pressure. The rest were either at atmospheric pressure or sub-atmospheric pressure. That's just to clarify that point .

The assessment of whether there was any infectivity in the meat and bone meal that were produced by these procedures was on the basis of injecting meat and bone meal into groups of

generally 24 mice and then looking for the development of spongiform encephalopathy. I also explained, and I was showing on that table, that the experiments were done in pairs representing minimum and average conditions, minimum average. Within the context of these, we titrated the amount of infectivity present when it was possible to do so, in the samples which represented the average conditions .

SO, for the protocols which represented the minimal conditions for any given process, we only did a qualitative assay. In other words, one group of 24 mice injected with meat and bone meal. For the quantitative studies for those protocols which represented the average procedures, we did proceed on to do titration. In other words, serial dilutions of that meat and bone meal to get a measurement endpoint.

Does that answer your question?

MR. FAITEK: No.

DR. TAYLOR: Shall I say it another way?

CHAIRMAN BROWN: What is it you want to know, Leon? Tell us again.

MR. FAITEK: Basically, what made you decide that there was infectivity in one case and

there wasn't infectivity in another case?

DR. TAYLOR: By the presence of disease in mice injected with the meat and bone meal from these procedures --

MR. FAITEK: From these procedures.

DR. TAYLOR: -- or absence of disease.

MR. FAITEK: Okay. Was the infectivity usually uniform if you injected 24 mice, that all 24 get them? In the other case when there was no infectivity, did none of the mice get it?

DR. TAYLOR: It varied. In the worst case conditions, 100 percent of the lowest -- group did go down. In other cases, you only had a proportion of the animals in such a group going down. Therefore, even in experiments where we only had one group of animals, if that group was only partially effected, you already had some indication that you actually reaching the down-turn on the titration curve. Whereas, with 100 percent infectivity with only a single group, you have no idea whether further dilutions -- two or three log dilutions further on would surely be infected. But in some cases, we did precise measurement and in others it was just a qualitative assay looking at 24 mice.

CHAIRMAN BROWN: IS that clear? In general, when you're trying to detect infectivity in what is called a bioassay, whatever it is you're testing, a specimen, you make a little suspension of it and you inoculate a little bit into the brain of a little animal. Often you use four or five animals -- inoculate the same specimen in -- certain and maybe that's all you'll do. You'll wait a year or six months and you'll see whether the animals die from what you inoculated.

Sometimes you'll want a little more precise answer than just "well, if you take the specimen and inoculate it per se", so you make a one to 10 dilution and another one to 10 dilution, and you go up. Then you wait your year again and you see, "well, every one of the six animals I inoculated with this specimen raw, died. Every one that I inoculated with a ten percent, a one to 10 dilution died." Then you get up to one to 1,000 and maybe four or five of the six die. Then you go a dilution more and maybe two die. You finally get up to a dilution where nobody dies. Suppose that is a one-millionth dilution, a million-fold dilution. If you have one death in an animal at that dilution, then you can sort of say, "well, in the undiluted,

there must have been a million infectious units. If I can dilute this specimen a million-fold and still have one animal die, I must probably have about a million units in the undiluted material. "

So, that gives you a little bit more precise idea of just how much infectivity you've got. If you just did the undiluted, then 15 out of 15 could die and you wouldn't know whether that represented just 15 infectious units or a billion infectious units. So that's the general idea of what infectivity measurements are all about. I don't know if that makes it clearer or not.

DR. HUESTON: Can I just add one thing, Paul, to help?

CHAIRMAN BROWN: Sure.

DR. HUESTON: So, if you measure and no animals die, that was the case in which David was sharing that none of the mice died --

MR. FAITEK: With undiluted material.

DR. HUESTON: -- with undiluted material at that last process. So, he was unable to detect any infectivity.

MR. FAITEK: But remember, there's a limit to how much of that material you can put in the mouse and that's the point that Paul Brown was

raising.

CHAIRMAN BROWN: Yes, that's the -- it's not difficult to detect and get a number for something that has infectivity. But if you want a rigorous answer to it doesn't have infectivity, then the total specimen would have to be inoculated. I did the arithmetic a long time ago and figured out that a six inch steak, for example, would require 10,000 mice to assay rigorously. We've just seen int he rendering experiment, it would take 24 million mice to do a rigorous experiment, so we never do that,

What we do as much as we can within the constraints of time, space and money -- and that's usually very imperfect. So, all we can say is we didn't detect infectivity. But you've got a much better handle on it if you inoculate 100 or a few hundred mice if you've got a specimen that's really important, that you really want to know. If you can even get up to five or ten percent, then you can use statistics to say what the likelihood is that it really is negative. These are the kinds of experiments that are not very often done because they're very, very expensive.

Yes ?

DR. SCHONBERGER: Following up on Fred Bader's model, it's not been run for tallow. It's been run for tallow derivatives. It has been run for tallow derivatives in the US, I gather? Is that right because part of the assumption for the 10^{-15} risk was a US sourcing of one in a million. I was wondering if you'd run it for, say, UK sourcing and maintained it in the derivatives? Has that been looked at?

The other issue is, how easy is it to run this model? Is it possible for some of these other issues that the Committee has been asked, to have those using your model and come up with some figures for us? Is that possible?

DR. BADER: The difference between Europe and the United States, again, in the US, we use roughly one in a million cattle. In Europe, we'd use one in 10,000.

DR. SCHONBERGER: I see.

DR. BADER: That 's the number we're using at the moment. So, it would raise it by two orders of magnitude. That' s -- using a paneuropean number, assuming that you're buying open trade region area.

From the standpoint of could the model

be used, you know, by this kind of Committee? I think the model is published. It's available. On the other hand, there is a workshop coming up in June that the FDA is sponsoring to look at other -- again, looking at the range of some of the assumptions going into some of these things. My guess is it might be good to wait until after one gets through that sort of thing and get more input into what the numbers are and assessments and sort of going into the model before one -- I mean, I think it's really up to this group to decide if they wanted to do something like that or not. We certainly would be willing to work with you.

CHAIRMAN BROWN: Yes, Ray?

DR. ROOS: Is there any reason to think that the assumptions that one would make for tallow in this country would be very different from the assumptions that you made for gelatin? Do you think that it would be approximately in the same location? I mean, what other assumptions are we making? There are some differences, I guess, with respect to temperature and alkaloid treatment, but I'm not sure that --

DR. SCHONBERGER : Well, he assumes that eight log reduction by processing. That may not --

DR. BADER: For tallow derivatives,

DR. ROOS: But that's the derivatives. Now, just with the tallow itself?

DR. BADER: It would be difficult for me to answer that. Maybe someone from the renderers could give a better estimate of that. The question is how different are tallow processes in Europe? One of the situations in the US that was mentioned is, we tend to have mega-industries where we have very large slaughterhouses that make, you know, major portions of the total supply for the US which, you know, run various processes. When you go to Europe, some countries have large slaughter operations. Some of them tend to have a lot of smaller slaughter operations. So, when you get into a lot of smaller operations, it's harder to know, you know, what the conditions really are. That's something that somebody would have to do -- European survey.

DR. ROOS: I thought we were just dealing with tallow in the United States for the moment.

DR. BADER: Okay. Then it seems to me the main issue is, you know, what's the difference in risk between processing of gelatin which we

reviewed the last time, and processing here? Do we have any data with respect to what the impact is with respect to that process and the risk? So, it may end up in approximately the same location as gelatin is what I would guess.

CHAIRMAN BROWN: If you wanted to say something -- Dave, what is -- and forgive me again. I should have this in my head, but I don't -- what did the FDA recommend with respect to gelatin, the source of which was strictly US raised animals? Strictly yours.

DR. ASHER: I don't have the text in front of me. No objection to gelatin from US or other non-BSE country with the exception that no CNS animals . Which, is I know, a debatable point that no animals with CNS disease should be accepted. That may be a moot point since they wouldn't be considered edible anyhow.

CHAIRMAN BROWN: Okay. The reason I asked, Ray, is that we're not going to be asked about evaluating the safety -- the processing safety, shall we say, of tallow vis-a-vis gelatin with US sources as exclusive sources. We're going to be asked let's presume that there's a risk of getting a little bit of -- or we're going to be

asked "do you think there is a risk of getting a little bit of the VSE agent into the mix?" So, we're not primarily concerned with a material that comes strictly from the US.

DR. ROOS: Well, I guess I understand that .

You know, getting back to something Leon asked in the beginning which was kind of reviewing the gelatin situation, I wonder whether there aren't similarities when one is concerned about gelatin sourcing from Europe in the same way as tallow sourcing from Europe? In other words, just as we might find an analogy and maybe a little bit of pressure on us to be consistent with respect to our recommendations now compared to what we did with gelatin in the past, in the United States maybe we should be consistent about what we felt about European sources as well.

CHAIRMAN BROWN: Oh, I think this is up for consideration tomorrow. I won't predict what the response is going to be, but certainly we can have in the back of our minds. When gelatin comes up, or maybe even before gelatin comes up, it might be a good idea for Dr. Asher to read to us what the FDA, in fact, recommended with respect to gelatin

just to refresh our memories.

DR. ASHER: Do you want to do it now?

CHAIRMAN BROWN, Yes, why don't we do it now? Not that we have to be slavish about this. I mean, we recommended slightly different things than the FDA, in fact, accepted and sent forward.

DR. ROOS: While David's doing that, I had one question. It really had to do with Dr. Taylor's results. That is, it seems to me that the data that we have now from Dr. Taylor shows what's the most safe method of rendering. In fact, that was used in order to change the policy in Britain with even recommendations about the whole European Union although there were some difficulties.

I just wondered, as long as we have the National Renderers Association individuals here, what they thought about -- how feasible something like that would be? In other words, for us to use the data that we have at present and what the risks are and the difficulties are with respect to following those guidelines which are based on the only data that we presently have.

DR. ASHER: This will be the main topic of the follow-up session on gelatin tomorrow. What I'm going to do is to read to you a summary that I

prepared simplifying the points that constitute FDA's policy at the moment. This policy is up for discussion tomorrow. It's the whole purpose for having a follow-up session tomorrow on gelatin. These things are not for the ages. We realize that they're going to change as the state of knowledge changes.

(1) Determine the tissue species and country origin of gelatin raw materials.

(2) Bones and hides of cattle showing signs of neurological disease should not be used to manufacture gelatin.

(3) Gelatin from bones and hides of cattle from BSE countries or countries of unknown BSE standards -- status according to OIE standards should not be used in injectable, implantable or ophthalmic products.

(4) At this time, Food and Drug Administration does not object to oral and cosmetic use of gelatin from bones of cattle from BSE countries if the cattle were from BSE free herds and if heads, spines, and spinal cords were removed directly after slaughter. The inclusion of the term "spines" was intentional.

(5) The FDA does not object to bovine

hide gelatin for foods and cosmetics if hides of cattle with signs of CNS disease were excluded and contamination of hides with CNS in eye tissues was avoided, or to the use of bovine gelatin from US animals or animals from other BSE free countries.

(6) Finally, the FDA does not object to the use of pig skin gelatin if it's uncontaminated with bovine materials from BSE countries or countries of unknown BSE status.

Tomorrow, there will be opportunity we hope for discussion of that policy.

CHAIRMAN BROWN: So, you see, that's pretty stringent. About all you could do more is to just Write off, let us say, a BSE country entirely, it seems to me. I mean, that's about as conservative and still allowing something to come in from a BSE country as I can imagine. So, pretty strict.

DR. ROOS: I mean, I may be mistaken but if we didn't have this rule, would this be exported from BSE countries, or are there limitations on gelatin exportation?

CHAIRMAN BROWN: I wouldn't guess that United Kingdom would object to exporting anything, would yOU? I mean, anything that comes from a cow

that they can, you know, send overseas.

DR. BRADLEY: Well, at the present moment, we're not allowed to export gelatin for food, cosmetic or pharmaceutical use that's been prepared from UK bovine materials.

CHAIRMAN BROWN: Whether or not the herd was BSE positive or not? In other words, period.

DR. BRADLEY: But scientifically, the best guarantees for gelatin -- for the whole world, could be that sourced from British cattle under 30 months old from which all the offals are removed and the skulls -- sorry, the heads and the vertebral column is also removed.

CHAIRMAN BROWN: And that's a UK regulation, not a European Commission regulation, is that right?

DR. BRADLEY: No, it's the European Commission regulation to us.

CHAIRMAN BROWN: Recommendation or regulation.

DR. BRADLEY: To us -- oh, no. No, no, not to our --

CHAIRMAN BROWN: So what you're saying is, today as we speak --

DR. BRADLEY: As we speak.

CHAIRMAN BROWN: '' in fact, gelatin coming from Great Britain under these circumstances may be, and probably is, safer than gelatin coming from Germany or Switzerland. Let's say country X.

DR. BRADLEY: It's all probably safe. But you're right, it might be a trade sight.

CHAIRMAN BROWN: Okay.

DR. BRADLEY: But could I just say also, just so it is in context, that gelatin can be manufactured from those said cattle as I've mentioned for industrial uses such as film making, and that can be exported. So, it's purely from the three categories I mentioned.

CHAIRMAN BROWN: What industrial use is -- well, this is gelatin again. We don't want to get into that.

Leon?

MR. FAITEK: You said you don't want to get into gelatin right now, so 1'11 hold off.

CHAIRMAN BROWN: Okay. Well, go ahead, ask.

MR. FAITEK: What I was going to say is that the extreme position that you had mentioned "writing off BSE countries", I thought is exactly what we had voted for. If I can read the question

as posed to us then, and that's reading from item 12.

The question was "does current scientific evidence justify continuing to exempt gelatin from restrictions recommended by FDA for other bovine derived materials from BSE countries?

CHAIRMAN BROWN: Yes, I think you just answered your two questions, the one you posed at the beginning of the day and this one. Yes, what the FDA recommended was basically what we suggested in our own advice. Therefore, we have good hopes that what we recommend tomorrow may also be followed. Generally speaking, the FDA pays attention to advisory committees. That's why they convene them. So, your presence here is meaningful, Leon.

Are there other questions from the Committee? Yes?

DR. LURIE: Just a question for Dr. Taylor.

As I understand from your article, there were two separate processes for tallow and each of those, there were 48 mice involved. Is that correct?

DR. TAYLOR: Yes, for the tallow

experiments.

DR. LURIE : Right, for the tallow ones. And in each of the two processes, zero out of 48 mice were infected, right?

DR. TAYLOR: Yes .

DR. LURIE: So the real question, it seems to me -- I mean, granted that zero out of 48 is the most likely estimate of how many were infected. The real question is what is the upper limit of the confidence interval around zero out of 48? Not having a computer in my head, I would guess it to be about three, perhaps even four percent.

So, what you've really done is, I think, given us greater than 95 percent confidence that the risk at that stage of processing does not exceed three or four percent. It does not say all that much about numbers like one or two, let alone, you know, 10^{-8}.

DR. TAYLOR: Yes, but the thing you have to ask, at the risk of what? It is what the assay -- the question assay is asking what is the risk of mice developing spongiform encephalopathy if I inject into the brain with tallow?

DR. LURIE: Right, right.

DR. TAYLOR: 1'11 show you some figures

tomorrow which you can possibly argue about. But if you equate that figure to what is known or speculated about difference of efficiency between intracerebral injection and oral dosing and what we know about species barriers, you can come up with a figure that says that the tallow injection experiments say to us that a human being would have to consume, all in one go, 16 kilograms of tallow to become infected.

CHAIRMAN BROWN: I don't think you two are arguing at all.

DR. LURIE: No, no.

CHAIRMAN BROWN: I mean, the question that you asked, the answer is affirmative. We don't have the Poisson calculation to give you that either, but that's precisely what -- that is absolutely correct. David's point is even granted that correctness, if you factor in other reducing factors, then you're even lower than it looks like.

Is that fair?

DR. TAYLOR: Yes.

DR. LURIE: Yes.

CHAIRMAN BROWN: Other questions? Yes?

DR. BURKE: As the new member of the Committee, I'm still a freshman in rendering school

here. so, you'll have to bear with me.

There are a number of checkpoints, as was said, in the way that materials are removed from the risk category. I can't make sense right yet as to whether or not there are any products in the United States which are used for parenteral use that either meet any one of these categories:

(a) That come from a high risk country from animals that have CNS disease;

(b) or where the head and spinal column are intact. And we've been talking a lot about the downstream things, but are there any products that meet any one of those criteria?

CHAIRMAN BROWN: Right . I think that's a very, very, very good question. It impressed me also that today was mainly downstream.

DR. BURKE: Right .

CHAIRMAN BROWN: Tomorrow, we're going to have to give major attention to upstream. So, that's a question that should arise again tomorrow. But if anybody wants to answer that today: are there any products that the FDA regulations, as we speak, permit entry into the US which, if they were, for example, a product from gelatin would not be permitted into the country? That's the question on

the table.

DR. BURKE: Or even not within the United States.

CHAIRMAN BROWN: I beg your pardon?

DR. BURKE: Even from products that were not imported, but a domestic one? Do we permit materials from bovines from the United States that have CNS disease?

CHAIRMAN BROWN: I think Dave just said no.

DR. BURKE: Well, he said that for some categories. I'm not sure he said that for everything. That's why I'm --

DR. HONSTEAD: Not for edible.

CHAIRMAN BROWN: Okay, not for edible.

DR. HONSTEAD: CNS animals don't -- well, there's -- people here, but for edible tallow, CNS affected animals are not slaughtered.

DR. BURKE: And then the last one is are there any parenteral materials that are used in which the skull and spinal cord are intact from US animals? The point being, what's the possibility there would be an undetected animal to get through the system? Would that be possible to still cause disease before we would recognize it?

DR. CHIU: Yuan-Yuan Chiu frOm FDA Center for Drugs.

The injectable we have -- approved by FDA, we have extensive list of all the products approved for marketing of investigational use. None of the products we have containing active ingredients derived from the CNS material. None of the products -- maybe I can not say none of the products come from BSE countries because we do have a product or two that comes from Germany. However, they're not from the CNS tissues.

All the injectable products, we look at to the source country. We look at the tissue types. We also look into the process. Then for high risk tissues in category two or category three, we also ask the manufacturer to do a certain kind of validation to assure there's a certain -- of the inactivation building, even though they're not coming from a BSE country. Just in case something happened, we would have a safety factor there.

Then with regard to injectable containing gelatins, we have probably more than two dozen products out there containing gelatins approved. Then we have a number of high investigational drugs. So, after we have the

guidance argument published, we have communicated with the companies and asked them to provide us with information where the source material comes from. So, we're working with the company to amend our applications to assure the sourcing will not be from BSE countries. SO, we're in the processing of doing that .

DR. BURKE: But it is possible that those injectable with gelatin could come from the United States from animals that were processed with the skull and spinal column intact, it went into the product, and/or were from animals which had CNS disease?

DR. CHIU: Most of the gelatin from pseudo grade gelatins are manufactured in Europe. So, most of them are not manufactured here. That' s why it takes time for us to sort it out. We're not very sure whether when they're manufactured in Europe, the CNS materials are removed even though the European Union now is proposing to have SRM removed but they have not been implemented yet. so, that's --

CHAIRMAN BROWN: All right, now I'm confused.

DR. BURKE: Yes, right.

CHAIRMAN BROWN: John, you said that in the US, gelatin which is going to go into oral preparations --

DR. HONSTEAD: And injectable.

CHAIRMAN BROWN: Well, that's the point. The question before was oral. All right. So, gelatin designated for oral use is never going to come from a brain sick cow, yes? That's an exclusion.

I thought you just told us that gelatin for oral use would never have a necrologic cow as part of its origin.

DR. HONSTEAD: Yes, I had my tallow hat on at that time.

CHAIRMAN BROWN: Okay.

DR. HONSTEAD: Now switching, gel bones usually come -- I'm fairly certain in the gelatin industry is here, but I think those are from edible carcasses as well. Edible carcasses don't have CNS diseases. Those are eliminated before they ever get into the slaughter plant.

Linda has another point.

DR. DETWILER: Yes, I can even go one step further. Now in the last year in conjunction with the FSIS and the renderers association and

APHIS that the -- well, first, to do the edible. The CNS condemns are kept out of the human food chain and the edible food chain.

Now when they're condemned, the CNS diseases -- and this would be adults, so I'll quality this, adult cattle condemned at slaughter. We have made an effort in the last year to do one of two things with those carcasses. One, have them incinerated right away after the samples were taken for diagnosis, or two, hold them, tag them until CNS disease and the TSE can be ruled out. That's what we're doing now throughout the country to rule out that possibility in cooperation with the renderers and FSIS.

CHAIRMAN BROWN: It might help the Committee tomorrow -- I think it would help me -- if we could get someone from the FDA to just give us a slide with a couple of examples, if they exist, of a situation in parallel between a source of gelatin and a product made from gelatin, and a source of tallow and a product made from tallow. I'm not entirely clear at the moment.

It looks to me as though the FDA currently is dealing with tallow, just as they are dealing with gelatin. That is that there are

restrictions from FDA countries. That was our business the last time. We took away the exemption that gelatin enjoyed with respect to BSE countries. It looks as though we're being asked a similar question with respect to tallow. Not an identical question, but a similar one.

DR. ASHER: There's no current exemption for tallow.

CHAIRMAN BROWN: Right. That's what I say, there's no current exemption for tallow. So, tallow currently is just like gelatin which has no exemption.

DR. CHIU: Right now there's no exemption for injectable gelatin because of the --

CHAIRMAN BROWN: Okay, well, this is the sort of thing that's very difficult for me to absorb by a microphone. I'd really like to see a couple of examples on a slide showing me the difference between a tallow and a gelatin product, injectable versus oral versus something else so that I can get a handle on what the situation with gelatin is now. If I were smarter, I'd have it all in my head. But it would help me a lot to see this kind of a comparison with two or three examples, so we know what we're dealing with a little more concretely.

I mean is everybody in the Committee clear on exactly what the situation with gelatin is, injectable, oral, cosmetic versus tallow?

DR. LURIE: I would take it further than that. I don't think we need two or three examples. I'm thinking of a fairly complicated table, really, that lists --

DR. BURKE: That's what I started to do here and that's what got me confused. I couldn't draw the table.

CHAIRMAN BROWN: So, it looks like we're all in the same boat. I'm afraid we're all human. I think the problem here is that the question and the subjects are similar but they're not identical. We're having a little trouble determining the differences. I think we could answer these questions if we didn't have to worry about gelatin lurking in the background ready to slay us if we make a mistake.

Is there a gelatin manufacturer in the audience who wants to make a comment?

MR. SALMONA: Thierry Salmona. I'm president of the GME.

I just wanted to make two comments to answer a question which was asked just one minute

ago. First of all, only animals found fit for human consumption having undergone ante and post mortem inspection are allowed to go into the gelatin raw material, okay? so, there is no possibly animal found diseased which can go into the raw material for gelatin, okay? This is true for the gelatin imported into the United States. It's also true for the gelatin made in Europe and sold in Europe, okay? It's a general rule applied by the gelatin industry, okay. That's number one, and it's mandatory in tallow.

CHAIRMAN BROWN: Is this all disease, or -- I'm sorry, was it any diseased animal?

MR. SALMONA: All disease, any disease. It's only animals found fit for human consumption in the slaughterhouse after ante and post mortem inspection by the official veterinarian service which are allowed to go into the gelatin manufacturing raw material.

CHAIRMAN BROWN: Are there any disorders, Will, of cattle which are thought to not compromise human suitability? I mean, does a cow have to be absolutely normal before it is considered fit for human consumption, or can he have a rash?

MR. SALMONA: It's just a cow which is

considered good for meat. Then it is considered good for gelatin, the same criteria.

CHAIRMAN BROWN: Right, and that's the point to my question.

DR. HUESTON: So, you're saying only materials from only edible carcasses are going in a gelatin manufacturer in Europe right now?

MR. SALMONA: Absolutely. Absolutely. This has been the case for years. Okay, there is no material which is not coming from an animal from which you can find your meat at the butcher shop which is going into the gelatin raw material. It's the same raw material as meat, except that we take bones and skins for gelatin and meat for meat. It's the same raw material, same animals. If an animal is discarded for meat, it's then discarded for gelatin. You can not use animals which are not considered good for human consumption to manufacture gelatin.

DR. HUESTON: Is there a gelatin industry then for non-edible?

MR. SALMONA: There is -- yes.

DR. HUESTON: And industrial gelatin --

MR. SALMONA: Yes. Yes.

DR. HUESTON: -- is that based from

materials coming from non-edible?

MR. SALMONA: Yes, practically yes.

DR. HUESTON: You're saying yes and one of your people in the audience is saying no, so I'm getting two messages.

MR. SALMONA: No, no, no. I'm sorry. The message is as following. There is gelatin which is made for industrial purpose: photographic gelatin, glue, matches, et cetera, et cetera. So, there are some uses which are not edible, okay?

In theory, for this gelatin, you could use different animals. In practice, what is happening is the same manufacturers import the same bones and therefore, also for this use, in the enormous majority of cases, these animals are found fit for human consumption as well.

DR. HUESTON: But the hides, are you telling me also that only hides from animals passed for human consumption are used in making gelatin, soft gelatin --

MR. SALMONA: In Europe, there is a regulation which prevents hides coming from the rendering circuit. So, hides coming from animals not fit for human consumption to go into what we call low risk factory, which are gelatin factories.

These hides coming from animals found diseased have to go in special factories in which there are basically not incinerated but transformed according to the rendering practices and then sterilized.

So, in Europe, there is a regulation which prevents these hides to go into the circuit. A tannery in Europe can not possibly accept material which is not coming from animals fit for human consumption. Because a tannery is not a high risk factory and we have this classification, high risk and low risk.

CHAIRMAN BROWN: Do the same guidelines apply to tallow?

MR. SALMONA: I'm sorry. I can not answer for tallow.

CHAIRMAN BROWN: Do the same guidelines apply to tallow?

MR. SALMONA: I can not answer to tallow. I'm not in the tallow business.

CHAIRMAN BROWN: Okay.

MR. SALMONA: I wanted to make a second comment to the question which is, it has always been the usage in industry to use material coming from country with no native case of BSE for parenteral use. Therefore, we have not made any comment in

this part of the guidance of the FDA because this has been common practice.

CHAIRMAN BROWN: Thank you.

Barbara?

MS. HARRELL: Okay, I would like for you to come back to the microphone, please?

When you said there was a post mortem done, is that done on each animal or a sampling, or a sample post mortem from maybe a herd that's come in? Is that on each animal?

MR. SALMONA: Each animal is inspected, okay, by the Veterinarian Service at the slaughterhouse, okay? Animals which are not found fit for human consumption are discarded and then their product and co-product can not be used for any use including gelatin.

CHAIRMAN BROWN: I'm curious -- I don't guess we have enough time to get into it. We're moving further and further and further back into the guts of the thing, no pun intended. I'm wondering about just what goes on when a veterinarian looks at a dead cow with respect to his suitability, or her suitability for human consumption?

DR. BURKE: Or a confused cow.

CHAIRMAN BROWN: No. Well, I assume

that this inspection is, I mean, like a USDA inspection. Or if a European inspection were occurring --

PARTICIPANT: Bob Brewer is here.

CHAIRMAN BROWN: Oh, yes, fine.

Just because we've got a little bit of time to play with, what would a packing house veterinarian be looking for?

DR. BREWER: Maybe I can do tomorrow morning's presentation now.

CHAIRMAN BROWN: Okay.

DR. BREWER: I don't have any slides so that would probably preclude me from doing it, actually.

Anyway, all animals are inspected in an ante mortem inspection in a USDA establishment and that's by the veterinarians, and that's all animals. Those animals are observed in motion and at rest. Then the animals are slaughtered and some of the animals -- 100 percent of the animals are inspected after they're slaughtered. If they pass the ante mortem inspection, 100 percent of them are examined on the post mortem. Now, in some of the large plants you have trained inspectors, lay inspectors under the supervision of the veterinarian making the

examinations . If the lay inspectors have a question about an animal, it's railed out and those are examined by a veterinarian. So, they all have 100 percent inspection.

To reiterate what most of you said, anything for edible tallow is from an animal that's been inspected and passed for human consumption. If it's rejected, in no way does it end up in edible tallow.

CHAIRMAN BROWN: Of course you're not, I'm sure, inspecting the brain or maybe you are --

DR. BREWER: No, we do not inspect the brain.

CHAIRMAN BROWN: I didn't think so, or you'd be looking like a pathologist in a hospital. He opens the body, the lungs look okay, the heart looks okay, the visceral look okay, the muscles aren't atrophy.

DR. BREWER: If that animal has any abilities moving around, or if it indicates it has a central nervous system on ante mortem, it is not slaughtered. It is condemned and everybody in the slaughterhouse. As Linda said, heads are now removed and the brains are sent to Ames, Iowa and they're examined histopathologically.

CHAIRMAN BROWN: In your experience, what sorts of things do you miss?

DR. BREWER: Do we miss?

CHAIRMAN BROWN: Yes .

DR. BREWER: I'm sure we miss a lot of things . There are about 33 million cattle slaughtered in the United States each year. We have about 110 million cattle in the United States. The vast majority of the product is coming from animals that are less than 18 months of age. As Don touched on, you've got a number of plants in the country now that are killing 5,000 or 6,000 head of cattle a day. That's a lot of cattle, but those cattle are extremely closely monitored when they're loaded on the trucks.

It's not uncommon to get in some of these big plants -- I know one plant that kills 35,000 head a week and they average one condemnation a week because they won't haul the cattle more than 50 miles to slaughter. They don't want them -- these trucks bring in the cattle all day. They no longer have 1,000, 2,000, and 3,000 head of cattle wandering around in the corral waiting to be slaughtered. Some of these plants only have the capacity to hold 400 head of cattle at a time, so

they're killing almost that many an hour. So, the cattle are coming in all day. They're loaded on the trucks in feed lots and brought in.

Now, I'm talking about the bigger plants, of course, obviously. I think by and large, this thing about how many cattle are missed that have the potential for BSE -- for the last ten years, there's been about 300 cattle condemned per year with central nervous disturbance on ante mortem. That's 300 out of 33 million cattle. This fluctuated just around that figure for at least the last few years.

CHAIRMAN BROWN: And you say these would be cattle that would be coming through and you would determine that in spite of the fact that they were sent to you, there was something wrong that might be neurologically related.

DR. BREWER, Right, right.

CHAIRMAN BROWN: So, the first screening, presumably, would be by the rancher himself who would --

DR. BREWER: Hopefully.

CHAIRMAN BROWN: -- yes, hopefully, would cull his staggering cattle. Then some would die, presumably, because they had a disease that

killed them before they came to market. And a few, as you say -- 300 out of -- what did you say?

DR. BREWER: Thirty-three million, possibly --

CHAIRMAN BROWN: -- would escape this and come to the attention of the inspectors.

DR. BREWER: And as I say, these animals are examined both in motion and at rest in the corrals prior to --

CHAIRMAN BROWN: Yes, right. Well, in terms of necrologic disease, since you don't examine the brain, it would have to be pre mortem.

DR. BREWER: Yes, exactly.

CHAIRMAN BROWN: Question, Kiki, or comment probably?

DR. HELLMAN: Yes. This has been a very interesting discussion about slaughter practices. I think the question you raised earlier, Paul, on the request of having a charge showing the sourcing and the end product use of some of the products that contained gelatin and tallow is well placed. We'll try to get that tomorrow.

I would just like to bring the Committee back to the task at hand, to clarify and perhaps summarize. At last October's meeting, we dealt with

gelatin. In our '93 recommendations and '96 recommendations, vis-a-vis a letter to the industry, we requested that materials from cows that had Originated, resided or slaughtered in BSE countries not be used in FDA regulated products. Gelatin was exempt from that. At the meeting in October, we recommended that that exemption be rescinded so that gelatin is now included under those original recommendations. There are certain considerations that are going to be clarified tomorrow.

With regard to tallow, tallow had been included in the initial recommendations both in '93 and '96. So, now what we are asking is that should tallow be -- should the restrictions on tallow be lifted somewhat, vis-a-vis the processing and the other quality control assurances that are being put in place with regard to tallow and tallow derivatives. SO, there --

CHAIRMAN BROWN: Yes, they're reversed. Yes, we're going in different directions.

DR. HELLMAN: -- are different questions. They're reversed. They're reversed.

CHAIRMAN BROWN: Yes, gelatin we were asked about the recision --

DR. HELLMAN: Right . That's right.

CHAIRMAN BROWN: -- and sort of talking about it. The focus of this is whether we should loosen it up.

DR. HELLMAN : Exactly. So that I don't think we want to confuse gelatin and tallow because they are different questions.

CHAIRMAN BROWN: Yes. Anybody want to ask a question about dura mater as long as we're --

DR. HELLMAN: While you have me here.

DR. CHIU: I would want to make a further clarification. Even though the question could be lifted the restriction, but the question could also be more restrictive. That would be you would require BSE free country, however the process has to be under certain conditions. So, that would pose additional restraint. So, it could go either way for tallow and tallow derivatives.

CHAIRMAN BROWN: Yes, I think that's a good point. We are not being guided to move in one direction or the other by the FDA. We could, as we've just heard, go in either direction or no direction at all. We could simply remain stable. But the wording is "justify a change". It could be a change to be more strict, less strict, or unchanged at all.

Yes?

DR. DETWILER: I just have one addition to Dr. Hellman's comments. The USDA does prohibit the importation of gelatin for use in animal feeds from BSE countries, or from high risk countries. So, the exemption is human products.

CHAIRMAN BROWN: Leon?

MR. FAITEK : That was exactly a pivotal point in our discussion in April. The issue then was do we want to treat products for human consumption any differently than we treat products for animal consumption, and the answer was no. No importation of gelatin from BSE countries, period. That was my understanding of the decision that we reached in April.

CHAIRMAN BROWN : Yes, it might have been a little more subtle than that. We didn't say no, no, no. We said put it in the same bag with everything else for FDA consideration.

MR. FAITEK: Well, for example, the example that Dr. Detwiler mentioned.

DR. DETWILER: No, he was just making a comment.

CHAIRMAN BROWN: Yes?

DR. BURKE: The numbers that you gave of

Drs. Taylor and Bradley earlier that there had been two million cattle that had been slaughtered. Of those, there were 170,000 were confirmed BSE cases. The others were slaughtered because they were part of herds? That's the first question. The second one is, could you comment on the experience in the UK on the sensitivity and specificity of a clinical diagnosis of BSE in a cow?

DR. BRADLEY: Well, that's quite a lot of questions here. Dealing first with the numbers. I haven't told you everything that's happening on BSE.

After the export ban was placed upon the UK by the member states, subsequently, there was a negotiation for release of the export ban. The first one, which is where the two million cattle came from, was the establishment of animals over 30 months which should be destroyed and their products not used for any purpose. In practice, some are incinerated immediately, but the capacity isn't sufficient to do that for all of them. Those that are not incinerated are first rendered and then they're stored in these big piles I mentioned this morning, pending incineration. That total is two million -- approximately a million a year. That's

the rough figure.

On top of that, there were two other sorts of culls, or three actually. One is just being developed at the moment. There was a requirement to cull animals in the birth cohort of cattle where one animal in a herd in that cohort had succumbed to BSE. For example, we know that within herd incidence is relatively low with BSE. Still over 30 percent of herds that have had a case have only ever had one case. So, it's a very low incidence disease within herds in a general way. But in that group of calves that was exposed, which five years later one animal got BSE, there might be another ten or a dozen calves still around on that farm or on other farms.

Now, this is a cohort cull which totally amounts to about 100,000 animals. Of course, the great difficulty is tracing these. But when they're traced, they follow the same route. Basically, they have to be destroyed and not enter any feed chain. SO, we're Up to about -- I think the figure is something over 50,000 that have been found and actually killed in Great Britain out of an approximate 100,000. But some of those animals that haven't yet been found have been killed for other

reasons. Either the farmers killed them anyway or -- and the farmer has gone out of business so you can't trace them anymore, or they've been trapped by the other scheme.

There is a third scheme wherein before the export ban, we were exporting calves from any herd to the continent of Europe, to other member states, about half-a-million a year. The rules were that they must not be offsprings of cattle with BSE and they must be killed in their country of destination before they were six months old. Then they would be for veal, of course, which would be for human consumption. There would be no offals removed from those animals in the importing country. Because this trade vanished, there's been compensation paid to destroy these as well. I can't remember just the exact number, but we're talking about hundreds of thousands of animals.

Finally on this, because of the potential for maternal transmission, this is a proposal to identify offsprings of cases born after the first of August, born in animals that developed BSE after the first of August 1996. And that's just sort of the beginning to try to find such animals and destroy them. It would remove just a few

hundred animals that potentially might come down.

DR. HUESTON: Can I interrupt for one second because I'm afraid you may be expanding the confusion.

CHAIRMAN BROWN: Yes, I think so.

DR. HUESTON: Just let me start by saying the 170,000, that is the total number of confirmed cases of BSE. It has nothing to do with any of these numbers you're hearing now.

CHAIRMAN BROWN: No.

DR. HUESTON: It's entirely different.

DR. BURKE: But it does go into the two million numbers?

DR. HUESTON: No, nothing to do with the two million.

DR. BRADLEY: No. No, no, no.

DR. HUESTON: The 170,000 is from the very beginning. From the first case that was identified to today, there have been 170,000 confirmed cases meaning they've examined the brain and confirmed the disease. All of these things that Ray is talking about now are preempted culls of normal, apparently healthy animals as a preemptive measure to speed up the down -- end of the epidemic and restore public confidence.

DR. BRADLEY: Absolutely so. But on top of the 171,000, these are the confirmed cases.

Now, your other question was the specificity of the clinical diagnosis.

DR. BURKE: Actually, I'm more concerned about the sensitivity of the clinical diagnosis.

DR. BRADLEY: Okay. Well, each animal that is suspected to have BSE is compulsorily slaughtered and the brain examined. Throughout the epidemic, the average confirmation rate is 85 percent which is really very good. Of the remaining 15 percent, about 45 percent very roughly -- say almost half -- have an alternative diagnosis. It can be all sorts of different things: cerebral listeriosis, tumors, abscesses, tape worms, et cetera, et cetera. The other 50 percent have no detectable lesions. This number, this percentage, 15 percent, is now declining.

DR. HUESTON: Yes, that's the predict -- that relates to specificities predicted by -- tests is 85 percent.

DR. BURKE: The reason -- I'm sorry for taking as much time on this as we are, but a lot of this goes into whether or not a diseased cow -- whether or not that adds anything at all to the

screening value of protecting the overall -- the materials that go into the processing. How sensitive is that for picking up an animal that might go into the pool? Specificity isn't the answer. Sensitivity is one --

DR. BRADLEY: no.

DR. HUESTON: And that was part of the justification for the ban on all animals over 30 months of age because based on the pathogenesis study, you could not detect these infected tissues. Well, the ban on specific infected tissues was based on the pathogenesis studies. So, it was to take out all tissues that could, in the extreme case of massive oral exposure, demonstrate infectivity. Those were removed from the whole manufacturing change. Then they carte blanche took everything over 30 months of age, which meant they took animals younger than what they could create the disease experimentally with this massive oral dose. That was the basis around it.

DR. BRADLEY: I think all these extra animals, of course, are not allowed to have any of their tissues used for tallow, gelatin or anything else, and that's the point. It's all a preemptive public health --

CHAIRMAN BROWN: Yes . They're now ashed, is that right?

DR. BRADLEY: Exactly

CHAIRMAN BROWN: Yes. It occurs to me if you gathered that ash and put it in suitable containers and labeled it as napalm, you could sell it to the US Navy and it could travel around the US incognito by train for the next ten years. I don't know if you know that story or not.

I think we can wrap things up. I'm glad we got some of these knotty problems brought up before the day is out. I'd prefer that they be introduced today than wait until tomorrow when I think, as is usual, we will come to the moment of truth and find ourselves still perhaps on the fence about one thing or another.

It is now 4:30. We will conclude today's proceedings now and convene again at 8:00 tomorrow morning.

DR. HONSTEAD: Paul, can I make one comment?

CHAIRMAN BROWN: Yes.

DR. HONSTEAD: One real brief comment to build on this excitement here. I think you can see how exciting and interesting it is to discuss TSE

risk. It's very, very challenging.

I also want you to realize that after this two days, the audience in this room is going to be some of the top experts on TSES among the world's population of people. So, you will have a great background in this. I challenge each of you to come to the symposium, the workshop on TSE risk at the University of Maryland in June, because you have a great deal to contribute now -- you will go home and think about this for a couple of months and it will even be better.

The organizers of the Committee are both here in the room. It's Dr. Will Hueston from the University of Maryland and Dr. Kiki Hellman from FDA. I think that this risk workshop can only build on these very issues that we're talking about.

CHAIRMAN BROWN: Thank you, John.

John used to be a scientist and he's now a public relations officer.

DR. FREAS: I would like to remind the Committee members that some of the material that was passed out today is confidential. I am required to take all the confidential -- anything left on the table and shred it. So, if you want the material, please take it with you.

(Whereupon, the meeting was adjourned at 4:24 p.m., to be reconvened at 8:00 a.m., the following day.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: Transmissible Spongiform Encephalopathies Advisory Committee Meeting

Before: Food and Drug Administration/PHS/FDA

Date : April 15, 1998

Place: Bethesda, Maryland

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