DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 589

[Docket No. 96N–0135]

RIN 0910–AA91

Substances Prohibited From Use in Animal Food or Feed; Animal Proteins Prohibited in Ruminant Feed

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the regulations to provide that animal protein derived from ruminant and mink tissues is not generally recognized as safe (GRAS) for use in ruminant feed, and is a food additive subject to certain provisions of the Federal Food, Drug, and Cosmetic Act (the act). The proposed regulations would establish a flexible system of controls, designed to ensure that ruminant feed does not contain animal protein derived from ruminant and mink tissues in a manner that encourages innovation. FDA is also considering alternatives to this proposed ruminant-to-ruminant prohibition, and is requesting comment on the relative merits and disadvantages of the alternatives. FDA is proposing this action because the feeding to ruminants of protein derived from potentially transmissible spongiform encephalopathy (TSE)-infective tissues may cause TSE in animals. TSE's are progressively degenerative central nervous system (CNS) diseases of man and animal that are fatal. Epidemiologic evidence gathered in the United Kingdom (U.K.) suggests an association between an outbreak of a ruminant TSE, specifically bovine spongiform encephalopathy (BSE) and the feeding to cattle of protein derived from sheep infected with scrapie, another TSE. Also, scientists have postulated that there is an epidemiologic association between BSE and a form of human TSE, new variant Creutzfeldt-Jakob disease (nv-CJD) reported recently in England. BSE has not been diagnosed in the United States. However, this proposed rule is intended to prevent the establishment and amplification of BSE in cattle in the United States, and thereby minimize any risk which might be faced by animals and humans.

DATES: Written comments by February 18, 1997. FDA proposes that any final rule that may issue based on this proposal become effective 60 days after the date of its publication in the Federal Register.

Submit written comments on the collection of information requirements by February 18, 1997.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857. Submit written comments on the information collection requirements to the Office of Information and Regulatory Affairs, Office of Management and Budget (OMB), New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, ATTN: Desk Officer for FDA.

FOR FURTHER INFORMATION CONTACT:

Regarding Scientific and Industry Issues:

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Regarding Procedural and Regulatory Issues:

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SUPPLEMENTARY INFORMATION

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I. Summary

A. Introduction

In the Federal Register of May 14, 1996 (61 FR 24253), FDA published an advance notice of proposed rulemaking (ANPRM) that solicited information and public comment on the issue of using protein derived from ruminants (cattle, sheep, goats, deer, and elk) in ruminant feed. The agency requested information and comment on a number of issues because it was assessing whether to prohibit the use of ruminant protein in ruminant feed. BSE has not been identified in the United States. The agency issued an ANPRM because of its concern about the possible adverse effect on animal and human health if TSE's were to be spread through animal feed. After reviewing the ANPRM comments and other sources of information, the agency is proposing to prohibit the use of ruminant and mink animal tissue in the feed of ruminants. Because TSE has been found in U.S. mink, the agency is also including mink tissue in the proposed prohibition. The agency is also considering alternatives to the proposed ruminant-to-ruminant prohibition, including the alternative of taking no action.

B. GRAS Status of Ruminant and Mink Tissues

The agency is proposing to declare that protein derived from tissue from ruminant animals and mink is not GRAS, by qualified experts, for use in ruminant feed and is therefore a ''food additive'' under the law. As a result, because neither a food additive regulation nor an exemption is in effect for ruminant and mink tissues intended for feeding to ruminants, such tissues would be deemed adulterated. Milk and gelatin proteins derived from ruminants, and blood from cattle are exempt from the proposed prohibition. The proposed rule does not apply to any nonprotein animal tissues such as tallow or other fats.

Expert opinion that the tissues are GRAS would need to be supported by scientific literature, and other sources of data and information, establishing that there is a reasonable certainty that the material is not harmful under the intended conditions of use. Expert opinion would need to address topics such as whether it is reasonably certain that BSE does not, or will not, occur in the United States; whether it is reasonably certain that the BSE agent will not be transmitted through animal feed, i.e., that the processed tissues are not infected by the agent, are deactivated by the rendering process or are not transmitted orally; and whether it is reasonably certain that the agent will not be transmitted to humans through consumption of ruminant products. ''General recognition'' cannot be based on an absence of studies that demonstrate that a substance is unsafe; there must be studies to establish that the substance is safe. Also, the burden of establishing that substance is GRAS is on the proponent of the substance. *See U.S.* v. *An Article of Food * * * Co Co Rico,* 752 F.2d 11 (1st Cir. 1985).

Although the ANPRM did not specifically ask for opinion on the GRAS issue, a number of comments from scientific organizations and individual scientists strongly suggest that the comments would support the view that ruminant and mink tissue is not GRAS when fed to ruminants. Some of these comments submitted data and information that would support such opinions. Only a few comments included statements by scientists, or scientific organizations, to the contrary. Similarly, the opinions stated by scientists who spoke during a 1996 symposium on TSE's would, in general, support the ''nonGRAS'' position. The symposium, ''Tissue Distribution, Inactivation and Transmission of Transmissible Spongiform Encephalopathies,'' was cosponsored by FDA and USDA, and was held in Riverdale, MD, on May 13 and 14, 1996.

FDA has searched for but has not found sufficient literature or other sources of data and information that would, on balance, support expert opinion that ruminant and mink protein is GRAS as a ruminant feed additive. Previous comments on the agency's proposal to prohibit the feeding of specified sheep and goat offal (59 FR 44584, August 29, 1994) did not include either written GRAS opinions from qualified experts, or data and information that would support such opinions. The relevant data and information, and lack thereof, are discussed more fully in this section, and in section II. of this document. See Section III.A., of this document, for a further explanation of ''GRAS'' and ''food additive.''

C. The ''No Action'' Alternative

Even when, as in this case, FDA has taken steps leading to a tentative determination that a substance added to food is not GRAS, the agency is not required to issue a proposal declaring that the substance is not GRAS and is a food additive subject to section 409 of the act. Section 570.38 provides that the agency may take such an action. The agency considered the possibility of not issuing a proposal with regard to the feeding of ruminant and mink tissues to ruminants.

The fact that the data and information do not document an immediate threat to the U.S. public health supports this ''no action'' alternative. Moreover, certain of the available data and information can be used to support the view that the threat, if any, is minimal.

The evidence suggesting that there is no immediate threat is summarized as follows. First, BSE has not been detected in cattle in the United States despite an extensive surveillance effort that has been in place for several years. Restrictions on the importation of cattle, cattle products and feed ingredients from BSE-affected countries are in place to minimize the possibility of BSE entering into the United States. Surveillance, training of veterinary practitioners and diagnosticians, and other efforts are in place to detect any occurrence of BSE quickly, and to minimize its spread among the cattle population. No empirical scientific evidence is available to establish that BSE will occur from any of the possible sources, such as transmission from another U.S. species in which TSE's have been diagnosed; spontaneous occurrence in cattle; or importation of live animals or animal feed products carrying the BSE agent. For example, transmission between any two species is difficult to predict, based on available data, because of variability in species barriers (Ref. 1).

Second, even if BSE did develop in the United States there is no conclusive scientific evidence that the disease would be spread through animal feed, the product that provides FDA's jurisdictional nexis. Although there is strong epidemiological evidence that the feeding of processed tissue from sheep containing scrapie to cattle caused the widespread BSE infections in the United Kingdom, many experts believe that the chances that the United States will have a BSE outbreak, similar to the epidemic that took place in the United Kingdom, are low. For example, most of the industry practices and other conditions believed to have been associated with the BSE epidemic in the United Kingdom do not exist in the United States. Further, the U.K. epidemiological evidence of transfer from sheep to cattle has not been confirmed by direct scientific data. This has caused some to question the assumption that the BSE originated from scrapie (Ref. 1). Further, some

experimental information suggests that the TSE's in general are not readily transferred by the oral route. Experimentally, the oral route has been suggested to be the least efficient means of transmission for TSE's (Ref. 1).

Third, the postulated connection between BSE and CJD has not been definitively established. Scientists have theorized an association between BSE and the recent appearance of nv–CJD in the United Kingdom. While the epidemiological association, both in time and geography, of these two diseases in the United Kingdom provides suggestive evidence of an association between the two, the available evidence does not establish causation. Although the BSE agent has been transmitted to laboratory animals, the species barrier between cattle and humans may be higher than between cattle and mice (Ref. 1). Epidemiological evidence linking BSE with classical CJD is even less supportive. Although CJD occurs in the United States, nv–CJD has not been reported in this country.

The FDA's conclusion that there is no immediate threat to the public health in the United States is supported by a statement from the World Health Organization (WHO) that the ''risk, if any, of exposure to the BSE agent in countries other than the U.K. is considered lower than in the U.K.'' (Ref. 2). A number of comments to the ANPRM made a similar assertion, urging that FDA's regulatory decision be made on the basis of scientific information and contending that the available information did not support the contemplated action.

D. The Basis for the Agency's Proposed Action

1. General Discussion

Even though there is no immediate threat to the U.S. public health and some information that indicates that a threat, if any, is minimal, after careful consideration the agency has tentatively concluded that regulatory action is necessary to protect animal and human health. The agency has reached that tentative conclusion because there is a growing body of data and information that affirmatively raises public health concerns.

The data and information raise concern that BSE could occur in cattle in the United States; and that if BSE does appear in this country, the causative agent could be transmitted and amplified through the feeding of processed ruminant protein to cattle, and could result in an epidemic. The agency believes that the high cost, in animal and human lives and economics, that could result if this scenario should occur, justifies the preventive measure reflected by the proposed regulation. Although the agency expects some continued voluntary reduction in the feeding of ruminant and mink tissues to ruminants, the reduction is not expected to be extensive enough to obviate the need for mandatory preventive measures.

Statements from several prominent public and animal health organizations support this proposal to regulate the feeding of ruminant tissues to ruminant animals. For example, the Centers for Disease Control and Prevention (CDC) has urged the agency to adopt a ruminant-to-ruminant feed prohibition (Ref. 3), and USDA has recommended the same action. Although WHO considers the risk in countries such as the United States to be minimal, that organization has nevertheless called on all countries to prohibit the use of ruminant tissues in ruminant feed (Ref. 2).

A number of comments to the ANPRM, including comments by several consumer groups, supported regulatory action by FDA. The Pharmaceutical Research and Manufacturers of America urged FDA to take all necessary steps to prevent an outbreak of BSE, and to prevent the potential spread of BSE should a case occur in the United States. One pharmaceutical firm emphasized the importance of acknowledging public perception, stating that a ruminant-to-ruminant prohibition would ''significantly decrease the concern regarding this perceived risk.'' Another pharmaceutical firm characterized the risk as ''small but real.'' A group of livestock producers, veterinary associations and scientific organizations cited the WHO recommendations to support their call for a voluntary ruminant-to-ruminant prohibition. The group stated that such a prohibition would ''eliminate any risk, no matter how remote [and would] totally prevent BSE from ever occurring in the United States.''

The agency is concerned about the public health issues raised but not resolved by the available scientific information. The fact that the causative agent or agents for TSE's have not been clearly identified, and their transmissibility has not been fully characterized, adds to the concern. However, certain information that is well documented supports the agency's decision as well. TSE's are 100-percent fatal diseases that have been diagnosed in humans and a number of animal species. The diseases are progressively degenerative CNS diseases that are characterized by a relatively short clinical course of neurological signs. TSE's have a prolonged incubation period, i.e., 2 to 8 years in animals, and scientific evidence supports the view that TSE's can be transmitted in the preclinical stage. There is no practical method to detect the presence of TSE's during the preclinical stage.

2. Analysis of Risk Factors

This section describes the evidence that supports the agency's tentative conclusion. The evidence relates to the risks that BSE could occur in cattle in the United States; that the BSE agent or other TSE agents could be amplified in the cattle population by the feeding of ruminant and mink tissues to cattle; and that the agent could potentially be transmitted to humans.

a. *The risk of BSE occurring in the United States.* BSE has not been diagnosed in the United States. FDA does not have evidence to support the theory that BSE already exists, undiagnosed, in this country. However, the agency does find plausible the arguments of the theory that BSE could develop in the United States from three possible sources: Transmission of TSE's from other susceptible species, spontaneous occurrence, and importation in live animals or animal products.

The evidence concerning transmission from other species is summarized as follows. TSE's other than BSE have been diagnosed in animals in the United States. These include scrapie in sheep and goats, transmissible mink encephalopathy (TME), and chronic wasting disease (CWD) in deer and elk. Feline spongiform encephalopathy (FSE) has been diagnosed in cats in other countries. In general, the TSE's have been shown to be naturally transmissible within species and are believed by some scientists to be naturally transmissible (as distinguished from experimentally transmissible), at least to a limited extent, between species. Consumption of meat and bone meal (the predominant animal tissue-containing product fed to animals) which was produced under conditions similar to the meat and bone meal which was implicated in the U.K. BSE epidemic, as well as the feeding of raw bovine tissue, also appeared to cause TSE in exotic cats and various zoo animals. This implies that the species barrier for BSE may be uncharacteristically low. (See e.g., Refs. 3 and 4). In addition to the epidemiological evidence relating to TSE transmission from sheep to cattle in the United Kingdom, there is limited experimental evidence of transmission

of the BSE agent from cattle to sheep. Many laboratory animal species have also been experimentally infected following the administration of tissues from animals with TSE disease.

There is some evidence to support the theory that BSE can occur spontaneously in cattle. The leading theory as to the causative agent, e.g., infectious protein or prion, inherently suggests that the BSE could occur spontaneously. Additional support arises from the fact that 85 percent of CJD cases are sporadic, and have no familial or identifiable link as to their cause. Recent surveillance information from Northern Ireland and Switzerland also supports the spontaneous theory. In these countries, BSE has occurred in cases in which no exposure to rendered protein can be found, and there is no evidence of BSE in the parental stock or herd mates of affected animals (Ref. 5).

As described more fully in section II.F.1.b. of this document, USDA–APHIS has implemented import restrictions on live animals and animal products from BSE-affected countries. As a result of the restrictions, the potential risk of BSE occurring in this country as a result of exposure from imported cattle and imported animal protein products appears to be small (Ref. 6). However, the risk from foreign sources of BSE introduction into the United States cannot be dismissed entirely because the USDA import restrictions are unlikely to be 100 percent effective even though no cases of BSE have been diagnosed to date in the United States. The USDA regulations are intended to reduce or control risk, not completely eliminate it. See e.g., 56 FR 63866, December 6, 1991.

b. *The risk of amplification in the cattle population.* Research has shown that various animal tissues can transmit BSE infectivity. There is also evidence supporting the view that the agent could be transmitted orally (e.g., through animal feed). Although some experimental evidence suggests that the TSE's in general are more readily transmitted by means other that the oral route, research also suggests that the BSE agent is more susceptible to oral transmission. In most cases (e.g., the U.K. epidemic) the natural route of exposure to TSE's including BSE is suspected to be oral. This belief is supported by the dramatic decline in BSE cases in the United Kingdom following implementation of the ruminant-to-ruminant feeding prohibition. In the United Kingdom, where more than 160,000 cases of BSE have been diagnosed, a 1988 ban on the feeding of ruminant-derived protein supplements to other ruminants was associated with a steady decrease in the disease incidence starting in 1993. The 5-year period between the initiation of the ruminant-to-ruminant ban and the decline in the incidence of BSE is consistent with the known incubation period in cattle of 2 to 8 years. Further, preliminary experimental data show that the BSE agent can be transmitted orally to cattle through feeding of material from an infected cow (Ref. 3). Thus, there is a chance that BSE could be spread in animal feed if it developed in the U.S. cattle population, whether spontaneously, from another species or by some other means.

The greatest risk factor for cattle may not be the single occurrence of a BSE case. Instead, the greatest risk may arise from the potential, given the prolonged incubation period, for unrecognized amplification of BSE in the cattle population, resulting in a potential for greater animal exposure. The possibility of risk from recycling ruminant tissues is enhanced by the fact that current rendering methods have not been shown, and are not expected, to completely deactivate the BSE agent, and that practical tests are not available for detecting either the BSE agent in rendered material or the presence of ruminant material in feed.

The preliminary experimental cow-to-cow TSE transmission data previously described occurred with as little as a single dose (one-time exposure) of 1 gram of brain material from the infected cow, indicating a low transmitting dose. This means, among other things, that FDA cannot determine the level of feed ingredients from animals tissues, if any, that is considered safe in ruminants.

c. *The risk of transmission of humans.* Finally, there exists the theoretical possibility of the transmission of a TSE in animals, such as BSE, to humans. CDC agrees that the link between BSE, and TSE's in humans, has not been fully demonstrated. Some of the ANPRM comments agreed. For example, one pharmaceutical firm stated that the evidence is not entirely conclusive. Nevertheless, a body of epidemiological and experimental evidence is developing to support the postulated association between BSE and nv–CJD. This and other scientific evidence developed more fully in section II leads the agency to propose for comment the prudent risk reduction regulatory action that is incorporated in the proposed rule.

E. Enforcement Provisions

The agency is issuing this proposed rule within the context of comprehensive government-wide efforts to minimize the risks previously described, and within the statutory authority provided to the agency. The proposed rule has two major components. First, the agency proposes to prohibit feeding animal materials derived from ruminant and mink tissues to ruminants, in the absence of a food additive regulation or investigational exemption. Thus, the prohibition would ensure that tissues which could contribute to a TSE epidemic by spreading the causative agent rapidly would not be allowed in ruminant feed.

The second component of the rule provides for a system of controls to ensure that the proposed rule would achieve its intended purpose. These provisions are necessary because limited controls are in place, or available, to prevent the spread of BSE through animal feed in the United States, should BSE occur. The proposed regulation places two general requirements on persons that manufacture, blend, process and distribute animal protein products, and feeds made from such products. The first requirement is to place cautionary labeling on the protein and feed products. The second is to provide FDA with access to sales and purchase invoices, for compliance purposes.

Firms that handle animal protein products from both ruminant and nonruminant sources, and that intend to keep the two kinds of products separate, would have certain additional requirements. These requirements would relate to the need for separate facilities or cleanout procedures; the need for standard operating procedures (SOP's); and in the case of renderers, their source of nonruminant material. Similar requirements would be placed on firms that handle animal feed containing animal protein products from both ruminant and nonruminant sources, and intend to keep the two kinds of feed separate. Requirements would be greater for the firms that intend to separate the animal protein products and feeds, because of the greater risk these operations would present for the possibility that ruminant protein might be fed, inadvertently, to ruminants.

However, the regulatory system would be flexible, allowing the regulated firms to innovate and choose the most cost-effective means of compliance. For example, some or all of the regulatory requirements previously described would not apply if any of the following innovations were developed and validated by FDA: Processing methods that deactivate the agent that causes BSE; test methods to detect the presence of the agent; or methods of marking or otherwise identifying the

material that contains ruminant protein. Further, the agency will consider modifying or revoking any final rule that is published prohibiting the use of ruminant and mink tissues in ruminant feed, if scientific and technical advances permit even greater flexibility than that offered in the proposed regulation. Conversely, the diagnosis of one or more cases of BSE in the United States, or new scientific findings, could lead to stricter regulatory requirements.

F. Alternatives

The agency is soliciting comments on several alternative means of minimizing the risk of transmitting TSE's in ruminant feed, in addition to the proposed ruminant-to-ruminant prohibition. These alternatives include:

(1) A partial ruminant-to-ruminant prohibition which would exclude all ruminant and mink tissues from ruminant feed except those bovine tissues that have not been found to present a risk of transmitting spongiform encephalopathy. Possible exclusions include slaughter byproducts from cattle that have been inspected and passed in inspected slaughter facilities, except tissues that have been shown through experimental trials and bioassays to transmit spongiform encephalopathy. Examples of the latter might include the brain, eyes, spinal cord and distal ileum. The agency solicits comments on the scope of this alternative;

(2) A prohibition on the feeding of all mammalian tissues to ruminants;

(3) A prohibition on the feeding of rendered material from those animal species in which TSE's have been diagnosed in the United States (sheep, goats, mink, elk, and deer);

(4) A prohibition on the feeding of specified offal from adult sheep and goats as proposed in 1994;

(5) Other alternative approaches that meet the agency's regulatory objectives and that might be suggested in comments to the proposed rule. The agency may in any final rule issued adopt such alternative approaches. Such alternatives may be more or less stringent than this proposal or may be a combination of provisions from this proposal and other alternatives. For example, one such option might be a proposal to exclude from the scope of any regulation certain facilities that apply specified risk-reduction measures in addition to, or in place of, those included in the regulation FDA is proposing in this publication. Therefore, the agency specifically requests comments on other approaches that would achieve the agency's regulatory objectives. Any proposed alternative approaches should be explained in detail, and their justification should be well documented. To the extent possible, please include information on costs and benefits of the proposals; and

(6) The ''no action'' alternative as it relates to this proposed rule. Again, detailed explanation and well-documented justification should be presented.

The agency's views on the advantages and disadvantages of these options appears in section V of this document. The agency invites comments on the relative merits and disadvantages of all these alternative concepts.

FDA has estimated that the annualized costs of the proposal, comprised of both the direct compliance costs and various indirect gains and losses, would range from $21.4 to $48.2 million. The agency also estimated that the annualized costs could range from $45.0 to $56.5 million for the mammalian-to-ruminant option; from $28.5 to $37.3 million for the partial ruminant-to-ruminant option; and would total less than $10 million for each of the remaining options. On the other hand, if the agency chooses the ''no action'' option and a BSE epidemic occurs, the above costs could be expanded by a great magnitude.

Because the body of scientific research related to TSE's is growing rapidly, the agency will place in the Docket copies of relevant scientific literature published after the agency completes work on this proposal, and before the agency completes work on any final regulation. The agency will add to the Docket, as appropriate, a brief statement of its assessment of the significance of the literature, and will invite comments. However, substantive changes from the proposed rule would be made in accordance with the discussions in the preceding paragraphs and the Administrative Procedure Act.

II. Background

A. TSE's

1. Scrapie

Scrapie is a slowly progressive, transmissible disease of the CNS in sheep and goats. Scrapie is characterized by a prolonged incubation period averaging 2 years, followed by a clinical course of 2 to 6 months when the animal exhibits sensory and motor malfunction, hyperexcitability, and death. The agent presumably moves from infected to susceptible animals by direct or indirect contact and enters through the gastrointestinal tract. Consequently, its spread appears to be both vertical (mother to offspring in utero) (Ref. 7) and horizontal (direct contact) between sheep (Ref. 8). Early signs of scrapie include subtle changes in behavior or temperament which may be followed by scratching and rubbing against fixed objects. Other signs include loss of coordination, weight loss despite a good appetite, biting of feet and limbs, tremor around head and neck, and unusual walking habits (Ref. 9).

The scrapie agent is found in lymphatic tissue (spleen, thymus, tonsil, and lymph nodes) in sheep with preclinical infections; however, in clinically affected sheep, the agent is identified in the intestines, nervous tissues (brain and spinal cord), and lymphatic tissues as determined by experimental infectivity studies in a susceptible animal model (Ref. 8). The brain has been demonstrated to have the highest level of infectivity of all tissues (Ref. 10).

Scrapie is known to have existed in Britain, Ireland, France, and Germany for over 200 years. It has been observed in the United States and Canada for about 50 years. The first case of scrapie in the United States was diagnosed in Michigan in 1947. From 1947 through January 1993, approximately 653 flocks have been diagnosed with scrapie (Ref. 11). At the present time, there are 67 known scrapie-infected flocks (flocks with sheep diagnosed with scrapie), and there are 8 known scrapie-source flocks (flocks to which scrapie-infected sheep were traced) (Ref. 12). In the absence of an antemortem diagnostic test, it is not possible to establish with absolute certainty that a flock is free of scrapie. Moreover, lack of reporting, the long incubation period, and open range husbandry practices in the western United States make it difficult to detect classical clinical signs and completely monitor scrapie in the United States.

2. BSE

BSE is a transmissible, slowly progressive, degenerative disease of the CNS of adult cattle. This disease has a prolonged incubation period in cattle following oral exposure (2 to 8 years) and is always fatal. BSE is characterized by abnormalities of behavior, sensation, posture, and gait. These signs are similar to those seen in sheep that are infected with scrapie. BSE is associated with spongiform lesions in the gray matter neuropil of the brainstem and neuronal vacuolization (Ref. 13). The clinical signs usually begin with changes in animal behavior, and may include separation from the rest of the herd while at pasture, disorientation, or excessive licking of the nose or flanks (Ref. 14). The most common history given by the herdsman was nervousness

or altered behavior or temperament, weakness associated with pelvic limb ataxia, paresis, and loss of body weight (Ref. 15). In some animals there are few gross pathological changes at necropsy associated with BSE other than the loss of body weight. However, postmortem histopathology of BSE distinguish it from other neurological disorders (Refs. 16 and 17). Neither vertical nor horizontal transmission has been documented for BSE.

BSE was first recognized as a new cattle disease by researchers at the Central Veterinary Laboratory of the British Ministry of Agriculture, Fisheries, and Foods at Weybridge, England in November 1986. As of November 15, 1996, BSE had been diagnosed in Great Britain in more than 165,000 head of cattle from more than 31,000 herds. Cases have been confirmed in 59.2 percent of the dairy herds and 15.3 percent of the beef herds (Ref. 18). The BSE epidemic curve for Great Britain peaked in January 1993 and is decreasing steadily, concomitantly with changes in rendering and feeding practices. BSE has also been reported in native cattle of Northern Ireland, Guernsey, Jersey, Isle of Man, the Republic of Ireland, Switzerland, France, and Portugal. BSE has been confirmed in cattle exported from Great Britain to Oman, the Falkland Islands, Germany, Denmark, Canada, and Italy.

There have been no cases of BSE in cattle in the United States. There has been one case of BSE in a cow imported into Canada from Great Britain. That cow was destroyed, along with its herdmates and other nearby cattle considered by animal health authorities in Canada to have possibly been exposed to the cow with BSE (Ref. 19).

3. Other Animal TSE's

Other animals have TSE's with typical characteristics of long incubation, neurological degeneration, and a 100-percent death rate. These animals include: Mink, elk and deer, zoo ruminants, and exotic and domestic cats.

TME is a mink disease with clinical signs and brain lesions similar to those of sheep infected with scrapie. TME is a rare disease in the United States. Since the disease was first recognized in 1947, in Wisconsin, four additional outbreaks have occurred in the United States. The last outbreak occurred in 1985 and was limited to a single mink ranch in Wisconsin (Ref. 20).

CWD of deer and elk is characterized by emaciation, changes in behavior and excessive salivation, polydipsia, and polyuria. The clinical course is from several weeks to 8 months, and the disease is invariably fatal (Ref. 20). From 1967 to 1979, CWD was observed in 53 captive mule deer in Colorado and Wyoming. Clinical signs were seen in adult deer and included behavioral alterations, progressive weight loss and death in 2 weeks to 8 months. Consistent histopathologic change was limited to the CNS and characterized by widespread spongiform transformation of the neuropil. The disease is a specific, spontaneously occurring form of spongiform encephalopathy (Ref. 21). Topographic distribution and lesion severity were most similar to those of scrapie and BSE. The duration of the clinical disease did not significantly influence lesion distribution or severity in either species (Ref. 22).

Scrapie-like encephalopathies have been described in certain zoo ruminants, i.e., a nyala, an Arabian oryx, and a greater kudu. Clinical signs included ataxia and loss of coordination with a short, progressive clinical course. Histopathological examination of the brains revealed spongiform encephalopathy characteristic of that observed in scrapie and BSE (Refs. 23, 24, and 25). Strain typing of the agent suggests that all of the cases are directly related to BSE.

Seventy domestic cats in the United Kingdom have developed FSE, a spongiform encephalopathy that was never previously reported. The cats all had progressive, neurological disease involving locomotor disturbances, abnormal behavior and, in most cases, altered sensory responses. Histopathological examination of the central nervous system revealed changes pathognomonic of spongiform encephalopathy; this included widespread vacuolization of the gray matter neuropil and neuronal perikarya (Refs. 26 and 27). Infective tissue from several of these cases, when injected into mice, resulted in brain lesions with a distribution and morphology that is undistinguishable from the lesions produced by BSE infective tissue injected into mice.

4. TSE's of Humans

The TSE's of humans are divided into specific clinical types, which may appear similar histopathologically but are either transmitted differently or demonstrate different patterns of distribution and prevalence.

a. *CJD.* CJD was first described in 1920 and 1921 when it was known as ''spastic pseudosclerosis'' or ''subacute spongiform encephalopathy'' (Ref. 28). The illness exists throughout the world and is claimed to have a similar prevalence in each of the countries tested with an annual incidence of approximately one case per million of the population. Autopsies are sometimes not performed on persons who may have died of CJD and many older people dying of a dementing illness do not have autopsies performed. There is an increased incidence among Libyan Jews (26 cases per million) and spatial or temporal clusters in areas of Slovakia, Hungary, England, the United States, and Chile. The average age of a typical CJD victim is 56 years of age, and only a few cases involving persons between 4 and 29 years have been reported prior to 1993. Between 4 and 15 percent of cases have a familial connection with other cases. There is a slightly higher incidence of CJD in women compared to men. Clinical prodromal symptoms start with changes in sleeping and eating patterns, and often include confusion, inappropriate behavior, vague visual complaints and/or ataxia. Those symptoms progress over a few weeks to a clearly neurological syndrome. A rapid onset of neurological symptoms appears in 20 percent of cases, most commonly myoclonic jerks and dementia with loss of higher brain function and behavioral abnormalities. The disease progresses with continued deterioration in cerebral and cerebellar function, and the onset of seizures. Ninety percent of the cases end in death within 1 year of onset. Diagnosis is by clinical assessment of patients and by examination of electroencephalogram patterns. Post mortem diagnosis is currently carried out by histological examination of cerebral tissue under the light microscope, although this is not always reliable. Research techniques that have been used to demonstrate CJD (and other TSE's) include electron microscopic examination of brain tissue extracts for scrapie-associated fibrils (SAF), immuno-staining of the tissue for prion-protein (PrP) antigens, western blotting of extracted PrP antigens and the intracerebral injection of tissue suspensions into test animals.

In some patients, the source of CJD has been claimed to be an infection transferred from other patients with the condition. For example, in one case, cerebral electrodes that had been sterilized with alcohol and formalin vapor after use in a patient with CJD, were used in the brains of two young epileptic patients, both of whom contracted CJD after a short incubation. The transfer of CJD by corneal transplant in 1 patient, by cadaveric dura mater grafts in several patients and by pituitary-derived human growth hormone injections in over 80 patients has also been reported.

Only the medical procedures described previously have been conclusively linked to transmission. The transmission of the disease from animal sources has been suggested; see further discussion in section II.C. of this document.

b. *nv–CJD.* A previously undetected new variant of CJD (nv–CJD) was reported by British scientists at a meeting of international experts convened by WHO on April 2 and 3, 1996 (Ref. 29), and published 3 days later (Ref. 30).

The major evidence for the existence of nv–CJD is the recognition of a new neuropathologic profile and the unusually young ages of 10 U.K. patients. Although all the cases had evidence of the pathognomonic spongiform changes characteristic of classic CJD, and therefore were appropriately classified as a form of CJD, the clinical course of the disease was atypical of classic CJD. The most striking and consistent neuropathologic feature of nv–CJD was the formation of amyloid plaques surrounded by halos of spongiform change. Plaques were extensively distributed throughout the cerebrum and cerebellum. Many of these plaques resembled those in kuru and were visible when examined by routine staining methods.

The temporal cluster of cases of nv–CJD in young patients (three were teenagers, five were in their twenties, and two were in their thirties at onset of disease) is highly unusual. Five of the eight deceased patients died before 30 years of age. (The expected annual mortality rate for CJD in persons under 30 years of age is less than five per billion.) The characteristic clinical features of the nv–CJD cases were: (1) A psychiatric presentation, (2) onset of a progressive cerebellum syndrome with ataxia within weeks or months of the initial presentation, (3) memory impairment with dementia in the late stages, (4) myoclonus, and (5) the absence of electroencephalographic changes typical of classic CJD.

Review of the patients' medical histories and consideration of various risk factors for CJD yielded no adequate clues as to the cause of this disease. The PrP genotype was determined for eight cases. The researchers noted that all genotypes were methionine homozygotes at codon 129 of the PrP gene. The research did not identify any of the known mutations associated with the inherited forms of CJD (Ref. 30).

Although scientists have stated that exposure to the BSE agent prior to the U.K. bans described in section II.F. of this document is the most plausible explanation for these findings, no clear epidemiologic link to BSE was identified. (See further discussion in section II.C. of this document.) Another potential explanation is exposure to TSE agents from animals other than cattle. Because the United Kingdom reinstituted epidemiological surveillance for CJD in 1990, increased surveillance is still another potential reason for the identification of this cluster of 10 cases of nv–CJD.

c. *Gertsmann-Strausller-Scheinker (GSS) syndrome.* GSS syndrome is an autosomal dominant condition in about 50 percent of siblings of reference cases (Ref. 28). The disease is similar to CJD except that it has a more extended onset and duration, a tendency towards cerebellar ataxia as the initial predominant neurological sign, and a large number of amyloid plaques present among the spongiform encephalopathic changes of the brain. The extensive distribution of amyloid plaques in the patient's brain is an observation shared by GSS syndrome and v–CJD. It has been transmitted to monkeys and rodents by intracerebral inoculation.

d. *Kuru.* Kuru is a condition of the Fore people of the Okapa district of the Eastern Highland in Papua New Guinea, in which a practice of ritual cannibalism of fellow tribesmen took place until approximately 1956 (Ref. 28). This TSE disease, which affected mainly adult women and children of both sexes, caused an annual disease specific mortality of approximately 3 percent. Most deaths of women in the tribe occurred through this disease. Some men who died from this disease were thought to have contracted it when they were young. Kuru may be transmitted by eating infected tissue or through open wounds. The brains of dead tribal members were eaten by women and children and the muscle tissue by men. The cohort of children born since 1957 have not suffered from kuru at all.

Clinically the disease causes a progressive cerebellar ataxia, uncoordinated movements, neurological weakness, palsies, and decay in brain stem function. Most patients dying of kuru are not demented, a major clinical difference between kuru and CJD.

e. *Fatal familial insomnia (FFI).* FFI is another inherited TSE-linked disease (Ref. 31). FFI is characterized clinically by untreatable progressive insomnia, dysautonomia, and motor dysfunctions. The disease often starts between 35 and 60 years of age and leads to death within 7 to 32 months. FFI is characterized pathologically by atrophy, neuronal loss, and gliosis in the anterior and dorsomedial nuclei of the thalamus (Ref. 32). FFI has been successfully transmitted to mice (Ref. 33), but not to primates.

5. Etiology

The cause of TSE's is controversial. The TSE agent: (1) Is presumably smaller than most viral particles and is highly resistant to heat, ultraviolet light, ionizing radiation, and common disinfectants that normally inactivate viruses or bacteria; (2) causes little detectable immune or inflammatory response in the host; and (3) has not been observed microscopically.

Resistance of the TSE agent to physical and chemical methods that destroy nucleic acid have essentially ruled out conventional microbiological agents as the cause. Currently, the infectious protein or prion theory is favored. Other proposed causes are an unconventional virus, consisting of virus-coded protein and virus-specific nucleic acid with unconventional properties, and a ''virino'' consisting of a core of nontranslated nucleic acid associated with host cell proteins (Ref. 34). Proposed causes of TSE's with less supporting evidence are: (1) Retroviruses (Ref. 35), (2) a spiroplasma (Refs. 36 and 37), (3) organophosphates (Ref. 38), and (4) peptide hormones (Ref. 39).

The prion theory suggests that the causative agent is a normal host protein (PrP or PrP–C) that is posttranslationally transformed into the causative agent or PrP–Sc. Transformation of the PrP can occur from rare somatic mutation of the prion gene, spontaneously or from contact with extraneous PrP–Sc. The spread of BSE in the United Kingdom is postulated to have occurred through the feeding of ruminant protein that contained the PrP–Sc protein and thus follows the portion of the theory that involves contact with extraneous PrP–Sc. This explanation requires that one accept that abnormal prion protein from sheep crossed the species barrier and resulted in BSE in cattle. An alternate explanation is that a spontaneous mutation or transformation or other nonorally induced event, occurred and resulted in undetected disease in a bovine. These explanations are not mutually exclusive and it is possible that both occurred.

Recent surveillance information from Northern Ireland and Switzerland tend to support the spontaneous mutation as a method by which BSE can occur. Northern Ireland has had more than 10 cows produce offspring, after the feeding ban, that developed BSE. Thus, 10+ cases are theorized to be spontaneous because there is no evidence of feeding meat and bone meal to the offspring and the dams are alive

and show no signs of BSE (Ref. 5). Switzerland, which has one of the most aggressive BSE investigational surveillance of any European Union (EU) country, has reported 205 cases of BSE. Some of these cases are in animals that were fed only grass and hay (Ref. 5). Regardless of how the initial cases occurred, however, the resulting unrecognized disease was amplified by the feeding of ruminant protein to ruminants.

Additional support for the feasibility of the TSE spontaneous mutation explanation is the fact that 85 percent of all CJD cases are sporadic and have no familial or identifiable link as to their cause. It is these cases that give rise to the very stable, 1 in a million per year, world wide incidence of the disease. DeArmond and Prusiner (Ref. 40), and Lansbury and Caughey (Ref. 41) have postulated that a noninduced somatic cell mutation or the spontaneous conversion of PrP–C into PrP–Sc are plausible explanations for the sporadic cases of CJD. DeArmond and Prusiner theorized that the 1 in a million

* * * may represent the combined probabilities that a mutation occurs in the PRNP gene, the probability that the mutation leads to the synthesis of the PrP–cjd (the abnormal protein), and the probability that the resultant PrP–cjd targets other neurons for the synthesis of more PrP–cjd at a rate fast enough to cause clinical disease in the patient's lifetime.

The etiology of human and animal TSE's are similar. Therefore the spontaneous mutation explanation cannot be dismissed with regard to BSE.

6. Pathogenesis

Following oral exposure of goats or sheep to the scrapie agent, the agent first accumulates in gut-associated lymphoid organs (tonsils and Peyers patches of terminal ileum) and later in other lymphoid organs, such as spleen and thymus, and finally in the spinal cord and brain (Ref. 8).

Likewise, in mice inoculated intra-peritoneally with the CJD agent, the agent localizes first in Peyer's patches and spleen, followed by the central nervous system (Ref. 42). The agent may enter the body through macrophages in the tonsils and domes over Peyer's patches in the intestine (distal ileum). The proposed routes of spread from the point of entry to other tissues and central nervous system are blood stream or nerve trunks. In experimentally inoculated animals, spread from the inoculation site in the eye of monkeys and peritoneum of mice has been shown to be by optic and splanchnic nerves respectively (Ref. 43).

Other investigators have demonstrated transient infectivity in the blood of experimentally infected laboratory animals, and naturally occurring infections of humans and mink, causing speculation that the agent is carried in the blood (Refs. 45 to 49). With one exception in serum (Ref. 50), all attempts to isolate TSE agents from the blood or milk of sheep or cattle have failed (Refs. 51 to 54). When TSE agents are injected intravenously into mice, the rate of clearance from the blood is extremely rapid (Ref. 55). In natural cases of BSE, infectivity has been found only in the brain, spinal cord, and eye; in experimental cases the agent has also been identified in the ileum (Ref. 56).

The question of disease mechanism remains open. Candidate mechanisms are the storage or accumulation of a large amount of abnormal PrP in the brain (Refs. 57 to 60), or insufficient amounts of normal PrP.

7. Transmission

There is little information about the natural transmission of TSE's of animals. In most cases the natural route of exposure to the TSE agent is suspected to be oral, although genetic disposition is known to play a role in sheep scrapie (Ref. 61). Investigators have suspected transmission of scrapie in sheep and goats by ingestion of placenta and have been successful in experimentally transmitting scrapie by feeding placenta to sheep (Ref. 62); however, genotyping of the PrP gene was not conducted.

In 1993, a study by Foster, et al., (Ref. 63) using a line of sheep in which natural scrapie does not occur demonstrated that sheep can be experimentally infected with BSE by intracerebral or oral administration. The intracerebral challenge resulted in five of six sheep developing the disease. The oral challenge resulted in one of six sheep developing the disease. Brain and spleen were recovered from the orally infected sheep and from one of the intracerebrally injected sheep. Goldmann, et al. (Ref. 64), confirmed that both sheep had the same PrP genotype. In 1996, Foster, et al. (Ref. 65) reported the results of injecting homogenized tissue harvested from these infected animals into a panel of mice. Transmission from the brains and spleen of both sheep gave incubation periods and pathology in mice similar to those seen in direct BSE transmissions from cattle to mice. Foster's work supports the position that BSE can cross species barriers by the oral route and that, when judged by the mouse bioassay, the disease manifested in sheep retains the incubation time and pathology characteristic of BSE rather than scrapie. However, the manifestation of BSE in the sheep is histopathologically and clinically indistinguishable from natural scrapie.

Information regarding the interaction of the TSE agents and the environment is limited. In 1964, Gordon reported the transmission of scrapie among bands of unrelated sheep on pasture. The mode of transmission was unknown (Ref. 66). In an effort to eradicate scrapie from Iceland a large area was depopulated of sheep and restocked with new sheep following a period of 3 years. Despite this effort, a few flocks of the new sheep developed scrapie; the origin was believed to be from scrapie that survived in the environment and not from reintroduction of the agent with the new sheep or through contaminated hay remaining on farms. However, a 1996 report suggests that six species of hay mites may be potential vectors associated with transmission of TSE's in Iceland (Ref. 67).

8. Genetics

There is a genetic component associated with several of the human TSE diseases. A specific point mutation at codon 178 is associated with fatal familial insomnia (Ref. 68). Point mutations at codons 102, 105, 117, 145, 198, and 217 are associated with GSS syndrome (Ref. 69). Point mutations at codons 178, 180, 200, 210, and 232 are associated with CJD (Refs. 68 and 70). Various insertions into the octapeptide repeat region of the PrP gene have also been associated with human TSE's (Ref. 71). It appears that the methionine/valine polymorphism at codon 129 may modify the phenotype and the transmission rate from GSS syndrome patients to mice (Ref. 72). No abnormalities in the sequence of the PrP gene in kuru patients were found.

There is also a genetic component associated with sheep scrapie. Point mutations at codon 171 of the sheep PrP gene are linked to the disease in the Corriedale, Lacaune, Romanov, Suffolk, and Texel breeds (Refs. 73 to 76).

An analysis of 370 cattle from Scotland revealed no difference between healthy cattle and cattle with BSE in the number of octapeptide repeat sequences (either five or six) and in a silent HindII restriction site polymorphism on the PrP gene (Ref. 77). No data were found that compared the sequence of the PrP gene of healthy deer, elk, mink, and goats with those afflicted by TSE's.

9. Diagnostics

Because of the long incubation period, the ability to diagnose the presence of a BSE infection prior to the onset of the

clinical disease would enhance the efficacy of surveillance and prevention programs. Because there is no fully characterized immune response to BSE or scrapie, diagnosis in live animals has been thought to be possible only when clinical signs are evident and must be confirmed by histopathology at post mortem (Ref. 10), or brain biopsy of moribund patients. Recently published research suggests antemortem tests for the TSE agent may be possible.

The observation of histopathological changes in the brain, such as vacuolization of the brainstem in BSE are positive indicators of disease (Ref. 78). Other available diagnostic tests are immunohistochemical staining and immunoblotting of the abnormal protein (Ref. 10). Detection and titration of the TSE agent can also be accomplished by intracerebral inoculation in mice or hamsters with a brain homogenate from a suspected animal. After an appropriate incubation period, the brain of the laboratory animal is examined for histopathological changes characteristic of TSE (Ref. 8).

The potential antemortem tests that have been published are described as follows: (1) Tests specific for PrP: (a) A capillary electrophoresis test (Ref. 79), and (b) a western blot test with increased sensitivity (Ref. 80); and (2) tests which identify metabolites of infected animals or humans: (a) A cyclic voltametric method which describes metabolites in urine (Ref. 81), and (b) an immunoblot test describing metabolites in cerebral spinal fluid (Ref. 82). Antemortem tests have not yet been validated for practical use.

Recent research has shown some promise for antemortem testing. Research by Shreuder et al. (Ref. 83), detected scrapie-associated PrPsc protein in tonsils from scrapie susceptible sheep about a year before the expected onset of the clinical disease. The research holds promise for preclinical detection in sheep, but needs further development. With regard to cattle, the researchers concluded that the technique may not work but is worth investigating. Research by Hsich et al. (Ref. 84), describes an experimental assay in humans and animals. The research found that a positive immunoassay in human dementia patients supports a diagnosis of CJD. The authors concluded that the assay may be helpful in premortem diagnosis of TSE in humans and animals showing clinical signs associated with TSE's. The validity of the test as a preclinical screen has not been established.

10. Inactivation

The agency considered requiring procedures for the manufacture of animal-derived proteins that would inactivate TSE infectivity. There have been several studies on the inactivation of TSE agents. The only broad generalization that can be drawn is that agents that denature protein can diminish the infectivity of the TSE agents. TSE infectivity does not appear to be markedly diminished by radiation or UV-light.

Recent research (Ref. 85) showed that 11 of the 15 rendering procedures tested produced meat and bone meal with no detectable BSE infectivity in a mouse bioassay. Only limited conclusions can be drawn about safety from these 11 procedures because the infectivity titer of the spiked starting material (which consisted of 10 percent brain) was several logs lower than that typically found in brain that is not minced and not stored at −20 °C. Also, the question of the adequacy of the mouse bioassay as the regulatory test which acceptably assures the absence of TSE infectivity to animals or man remains to be answered through future research investigations.

The four procedures that failed included two protocols using continuous vacuum rendering of high fat material and two protocols using continuous atmospheric rendering of natural fat material. The continuous vacuum rendering processes that failed were 120 °C for 20 minutes at a vacuum of 0.38 bar and 121 °C for 57 minutes at a vacuum of 0.4 bar. The continuous atmospheric rendering processes of natural fat material that failed were end temperatures of 112 and 122 °C after 50 minutes; however, end temperatures of 123 and 139 °C after 125 minutes both inactivated the BSE agent. Unexpectedly, the BSE agent was inactivated by three wet rendering processes that only reached a maximum temperature of 119 °C with a cooking time of 240 minutes, a maximum temperature of 101 °C with a cooking time of 120 minutes, and a maximum temperature of 72 °C with a cooking time of 240 minutes under a vacuum of 0.85 bar.

Preliminary, unpublished results indicate that the only rendering process which completely inactivates the scrapie agent (which was spiked with higher infectivity than that in the BSE experiments described in this section) is batch rendering under pressure (Ref. 86). The agency encourages more research in this area.

B. The Association Between Scrapie and BSE

Epidemiological studies of the outbreak of BSE in the United Kingdom, including a computer simulation of the BSE epidemic, have characterized it as an extended common-source epidemic. Each case has been considered a primary case resulting from exposure to a single common source of infection. It is believed in the United Kingdom that rendered feed ingredients contaminated with scrapie infected sheep, or cattle with a previously unidentified TSE, served as the common source of infection. One study demonstrated that meat and bone meal could be incorporated into cattle feed in sufficient quantity to transmit BSE to some of the animals that consumed the feed (Ref. 87). Thus far, other research including research by USDA has not confirmed that the feeding of U.S.-origin scrapie-infected feed ingredients to cattle produces BSE. Therefore, the theory that BSE evolved naturally in cattle has not been ruled out (Ref. 88). See also the discussion in II.A.5. of this document.

Furthermore, the U.K. studies suggest that the spread of BSE appeared to have been exacerbated by the practice of feeding ingredients from rendered BSE-infected cattle to cattle, including young calves, a practice that was subsequently banned. Incomplete immediate compliance with the feeding ban may account for the fact that some cattle born after the ban continue to be infected with BSE and has complicated any theory of vertical transmission of the disease. The research findings of maternal transmission of BSE are inconclusive, but if it occurs, it does so at a rate insufficient to maintain the epidemic (Ref. 89).

C. The Association Between Animal TSE's and Human TSE's

All the animal and human TSE's have been shown to be transmissible experimentally to laboratory animals. The human and animal diseases are pathologically similar and share some etiological similarities. TSE's are not officially considered zoonotic diseases, i.e., known to be naturally transmissible from animals to humans. The distribution of CJD in the world does not coincide with that of scrapie in sheep or of BSE in cattle. Human exposure to sheep or cattle has a low correlation with CJD. However, the recent report from the United Kingdom of nv-CJD, and its possible relationship to BSE, is causing scientists around the world including those at CDC to

reevaluate whether BSE may be a zoonotic disease.

This concern is further supported by the recent report of experimental BSE transmission to macaques, with the development of nv-CJD-like plaques in these monkeys (see the following discussion in this section).

The possibility of transmission of TSE's from animals to humans has been suggested, most recently in connection with the identification of nv–CJD in the United Kingdom. Scientists in the United Kingdom concluded that the nv–CJD cases may be unique to the United Kingdom, raising the possibility that they are causally linked to BSE. The scientists stated that ''the common neuropathological picture may indicate infection by a common strain of the causative agent, as in sheep scrapie in which strains of the disease have been identified * * *'' (Ref. 30). The United Kingdom Spongiform Encephalopathy Advisory Committee (SEAC) stated that ''although there is no direct evidence of a link, on current data and in absence of any credible alternative the most likely explanation at present is that these cases are linked to exposure to BSE before introduction of the SBO [specified bovine offal] ban in 1989'' (Ref. 90). A WHO consultation in April 1996 concluded that ''a link has not yet been proven between v–CJD in the U.K. and the effect of exposure to the BSE agent. The most likely hypothesis for v–CJD is the exposure of the United Kingdom population to BSE'' (Ref. 2). However, a second WHO consultation, in May 1996 concluded that ''the clinical and neuropathological features of the newly recognized CJD variant do not provide information which could be used to prove the possible link between this disease and BSE in cattle'' (Ref. 91).

The recent finding of florid amyloid plaques in the brains of macaques inoculated with suspensions of BSE-infected cow brains increases suspicion that exposure to the BSE agent may be the source of nv–CJD. Amyloid plaques have never before been seen in monkeys with TSE's, and the florid plaques resembled those in nv–CJD patients (Ref. 92). In a recent paper by Collinge, et al. (Ref. 93), it is stated that ''strains of transmissible encephalopathies are distinguished by differing physicochemical properties of PrPsc, the disease-related isoform of prion protein, which can be maintained on transmission to transgenic mice. 'New variant' CJD has a strain characteristic distinct from other types of CJD and which resembles those of BSE transmitted to mice, domestic cat and macaque, and is consistent with BSE being the source of this new disease. Strain characteristics revealed here suggest that the prion protein may itself encode disease phenotypes.''

The possible association between BSE and nv–CJD may be further clarified by results from studies that are under way (e.g., experimental inoculation of brain tissue from the nv–CJD patients into mice).

D. Infectivity of Specific Tissues

The WHO in a recent publication has summarized the infectivity of various tissues from sheep, goat, and cattle (Ref. 94). Scientific studies are currently being conducted in which calves are fed homogenized brain tissue from United Kingdom cattle confirmed to have BSE, and then various tissues are collected from the calves at 4-month intervals (Refs. 56 and 95). The tissues from these calves are being analyzed for the presence of the BSE agent. The study has been in progress for 18 months and only brain, spinal cord, and retina have been shown to be highly infectious. Distal ileum has been shown to be infectious, but much less than the previously mentioned tissues. No other tissues, most notably, muscle meat, milk, or blood have been shown to be infectious. The results of these current experiments parallel the previous research as summarized by WHO. However, the agency notes that infectivity of other tissues that might be fed to ruminants has not been definitively determined. This is, in part, because of the lack of desired sensitivity in the available assay methods.

In summary, meat, milk, milk products, and blood have not been shown to transmit BSE infectivity. These products are considered safe for human consumption by health authorities including the WHO.

E. Potential Risk of TSE's to the United States

1. Overview

This proposed FDA action is designed to reduce the risk of a BSE epidemic in the United States and thereby protect the health of animals and possibly of people if there is, in fact, a zoonotic relationship between BSE and CJD. Risk is defined as the probability of an adverse effect to an individual or a population. The four steps that are typically involved in risk analysis are hazard identification, hazard exposure, dose response, and risk characterization.

While BSE has not been found in the United States, the agency believes it presents a potential risk to the health of animals and people. There are incubational and symptomatic similarities (as well as several differences) among the TSE's. The scientific characterization of these diseases is incomplete. However, interspecies cross-infections have been scientifically demonstrated by parenteral injection and oral routes of exposure.

The typically long incubation period and the potentially devastating effect that a BSE outbreak would have on animal health and U.S. agribusiness also supports a conservative regulatory approach aimed at prevention. While the current level of exposure to products derived from animals with a TSE is extremely low or absent, the potential consequences of such exposure and the apparent small intake of the agent needed to achieve infection in some animals further encourage a conservative regulatory policy.

Dose response assessments will be difficult because of the lack of good exposure data and the possibility of different susceptibilities, e.g., age or genetic factors, in different subpopulations. Although the TSE's are generally transmissible to laboratory animals following intraperitoneal (ip) or intracerebral (ic) routes of administration, the limited data that are available following the oral route of administration suggests that this route is much less efficient than ip or ic. Currently, it is quite difficult to make an accurate dose response assessment for a TSE agent following oral administration.

A number of actions, in addition to this proposed rule, have been taken to manage a reduction in risk that BSE will enter the United States cattle population. Restrictions have been placed on the importation of live cattle (July 1989) and ruminant products (e.g., meat and bone meal, bone meal, blood meal, offal, fat, and glands) from countries which have BSE. Live animals imported prior to the restrictions on imports have been regularly monitored by Animal and Plant Health Inspection Service (APHIS) veterinarians, and APHIS is currently in the process of purchasing the remaining live cattle for diagnostic research purposes. Histopathological examination of brain tissues has been carried out on more than 5,000 specimens from cattle that were disabled or that demonstrated neurological signs prior to slaughter or on the farm, e.g., nonambulatory or rabies-negative cattle. Histopathological and immunohistochemical examination of the nonambulatory or ''downer'' cows has been carried out since 1993. There has been no finding of BSE in tissues from these animals. These animals represent the highest BSE risk in the country, however, they also represent an extremely small percentage of the cattle

slaughtered in the United States. This active surveillance program is continuing and may be expanded. The expansion of this program was indirectly supported by a comment to the ANPRM that all ''downer'' cows should be examined for BSE.

Voluntary actions by industry have reduced the feeding of rendered sheep proteins to ruminants and the rendering of adult sheep. A voluntary Scrapie Flock Certification Program was implemented in 1992. The program, a cooperative effort among industry, State animal health officials and APHIS, seeks to reduce the prevalence of scrapie in U.S. sheep. A considerable educational effort continues to increase the awareness of veterinarians, veterinary laboratory diagnosticians, livestock and related industry businesses, and producers to the early clinical signs of BSE. Videos of United Kingdom BSE affected animals have been distributed to USDA veterinarians to enhance their ability to clinically diagnose BSE in suspect live animals. CDC has recently published an update (Ref. 96) of its previous review of national CJD mortality and the results of active CJD surveillance in five sites in the United States. These reviews did not detect evidence of the occurrence of the newly described variant form of CJD in the United States. As an important complement to these other public health efforts, this proposed rule would declare that animal protein derived from ruminant and mink tissues is an unapproved food additive for use in ruminant feeds, and would establish enforcement procedures. These actions, individually and collectively, contribute to a greatly reduced risk of a BSE epidemic ever occurring in the United States.

2. Comparison With the U.K. Conditions

Investigators have identified several major risk factors that apparently contributed to the emergence of the disease and the resultant epidemic in the United Kingdom. These are: (1) A large sheep population relative to the cattle population, (2) a large, uncontrolled, scrapie incidence rate, (3) the production of ''greaves,'' an incompletely processed intermediate product in the rendering process, (4) changes in rendering processes, such as the reduced use of solvent extraction, and (5) the feeding of significant amounts, up to 4 percent of the diet, of meat and bone meal to young dairy calves.

In addition to the risk factors described in section II.E.2. of this document, the practice of processing dead sheep and cattle in the United Kingdom likely contributed to the amplification of the TSE agent. In the United Kingdom, sheep which may have died of scrapie and cattle with BSE, were picked up by ''knackers'' for rendering into animal feed. This material was partially rendered into ''greaves,'' which might have contained large amounts of the scrapie/BSE agent, and was fed to dairy calves in large amounts. The spread of BSE appeared to be facilitated by the feeding of rendered BSE-infected cattle back to calves. The BSE agent is postulated to have recycled from cows to calves through ruminant-to-ruminant feeding until the practice ceased following the 1989 ban on the practice.

In the United States, the cattle population is much larger than the sheep population, the incidence of scrapie is much lower and a scrapie control program is in place; renderers in the United States do not manufacture greaves; and the rendering processes used in the United States are thought to reduce the titre (level) of TSE agents if any. The lack of a practice of feeding large amounts of meat and bone meal to calves in the United States, and the comparatively younger average age of U.S. dairy cattle are also differences that are believed to be important in protecting the United States against a U.K.-type BSE epidemic. Nevertheless, scrapie does exist in the United States, sheep are rendered and included in ruminant feed, the rendering process does not totally inactivate TSE agents, and calves are fed meat and bone meal. Therefore the risk of a BSE epidemic in the United States, while much less, cannot be completely discounted.

F. Historical Efforts to Control TSE's

1. U.S. Actions

a. *FDA.* FDA is the Federal agency responsible for the safety and effectiveness of a large number of products and commodities. Briefly, these include, drugs for use in people and animals, human biological products, medical devices, food, dietary supplements, cosmetics, and animal feeds. Each of these product groups provides the potential for the transmission of spongiform encephalopathies in man or animals. FDA formed a Working Group composed of the Deputy Commissioner for Operations and representatives from the Centers to consider TSE's in relation to FDA regulated products. As a result of the Working Group's deliberations, FDA has taken the following actions:

- In 1992, letters were sent to manufacturers of dietary supplements asking those manufacturers to reformulate their products to be certain they do not contain materials from BSE or scrapie infected animals;
- In 1993, letters were sent to manufacturers of drugs, biologics, and devices asking them not to use bovine-derived materials from countries with BSE; and
- In 1996, letters were sent to manufacturers of drugs, biologics, devices, and animal feeds noting a possible relationship between BSE and nv-CJD and asking that they not use materials from BSE countries.

In 1992, FDA conducted a survey of major sheep rendering plants to determine compliance with a 1989 voluntary industry ban on the use of adult sheep offal in ruminant feeds. The voluntary ban and results of the survey are described in section I.F.3. of this document. In the Federal Register of August 29, 1994 (59 FR 44584), FDA published a proposed rule proposing to declare that specified offal from adult sheep and goats is an unapproved feed additive in ruminant feed (hereinafter referred to as the August 1994 proposed rule). In the Federal Register of May 14, 1996, FDA published an ANPRM stating that FDA was considering whether to provide that the use of protein derived from ruminants in ruminant feed be prohibited.

An international symposium entitled ''Tissue Distribution, Inactivation, and Transmission of Transmissible Spongiform Encephalopathies'' and cohosted by APHIS and FDA's Center for Veterinary Medicine (CVM) was held on May 13 and 14, 1996, in Riverdale, MD. The symposium participants engaged in discussion of findings from unpublished, recently completed, and in-progress scientific investigations on TSE's, and optimal approaches to managing any risk of TSE's to animal health.

b. *USDA.* USDA policy has been both proactive and preventive. The Food Safety and Inspection Service (FSIS) and APHIS have been active in taking measures in surveillance, prevention, and education about TSE's. In 1990, APHIS created a BSE Issues Management Team to analyze risks of BSE to the United States, disseminate accurate information about the disease, and act as a reference source for responding to questions about BSE. APHIS has also collaborated in the education of veterinary practitioners, veterinary laboratory diagnosticians, industry and producers on the clinical signs and pathology of BSE.

APHIS has increased its surveillance efforts to verify that the United States is free of BSE and to detect the disease should it be introduced into the United

States. As part of an ongoing active surveillance program, more than 60 veterinary diagnostic laboratories across the United States, and the National Veterinary Service Laboratories (NVSL) of APHIS, continue to examine bovine brains from the following sources: (1) APHIS investigations in the United States where suspected encephalitic conditions in cattle are reported under the foreign animal disease investigation program; (2) CDC and State public health laboratories (specimens from bovine that were found negative for rabies); and (3) FSIS (specimens from ''downer'' cows or those exhibiting CNS abnormalities). More than 5,000 bovine brains have been examined, and none of these specimens contained lesions with the characteristics and distribution typical for BSE (Refs. 12 and 97). APHIS is currently in the process of purchasing the 69 living cattle (from a total of 496 cattle) imported from the United Kingdom between 1981 and 1989. In July 1989, the importation of live ruminants and ruminant products from all countries known to have BSE in native animals was banned.

USDA continues to analyze and report epidemiologic findings and potential risks to the United States. In 1991, USDA issued two reports analyzing risk factors associated with BSE in the United Kingdom based on the British hypothesis of the disease occurring as a result of feeding scrapie-contaminated meat and bone meal (Refs. 98 and 84). Because of some similarities in the animal industries between the two countries, the possibility of BSE occurring in the United States could not be eliminated. However, the probability of occurrence was determined to be very low as the amount of sheep offal was found to be 0.6 percent of all U.S. rendered product compared to the estimate of 14 percent of all U.K. rendered product. Furthermore, the incidence of scrapie in the United States is much lower than in Great Britain; a scrapie eradication or control program has been in effect in the United States and rendered products are not routinely incorporated into calf diets as was the practice in the United Kingdom.

Since 1991, USDA has closely followed scientific findings and has updated the BSE risk factor analysis, first in 1993 (Ref. 99) and as recently as February 1996 (Ref. 4). Changes within each of the risk factors have been evaluated, and because there has either been no change or a decrease in the magnitude of risk factors, the overall risk of BSE in the United States is believed to have decreased. The February, 1996 report estimated the maximum potential 1-year period prevalence of BSE to range from 2.3 to 12 cases per 1 million adult cattle. In other words, under the worst case scenario between approximately 115 and 600 adult cattle would become infected with BSE each year, in a U.S. population of nearly 50 million adult cattle.

APHIS has had a scrapie control program in effect since 1952. Flocks that have been enrolled in the voluntary certification program for sheep for 5 years, and have not had a diagnosed case of scrapie within 5 years or a case traced back to the flock during that period, may apply for APHIS certification and be officially identified as such. This new control effort provides a mechanism to recognize flocks as scrapie-free in the absence of a live animal diagnostic test.

There is no official USDA program on TME or CWD. Although the last TME case detected in the United States was in 1985, monitoring for this disease continues. APHIS cooperates with State wildlife and diagnostic officials in Colorado and Wyoming in the limited areas where CWD has been reported.

In December 1991, APHIS placed a ban on importation of certain products of ruminant origin from countries known to have BSE (56 FR 63865, December 6, 1991). These products include: Meat and bone meal, bone meal, blood meal, offal, fat, and glands. In addition to prohibiting the materials listed previously, the regulation requires that imported meat for human or animal consumption from bovines be deboned, with visible lymphatic and nervous tissue removed; that it be obtained from animals which have undergone a veterinary examination prior to slaughter; and that it be obtained from ruminants which have not been in any country in which BSE has been reported during a period of time when that country permitted the use of ruminant protein in ruminant feed. APHIS may allow the importation of the banned products under a special permit for scientific or research purposes, or under special conditions to be used in cosmetics. No bovine meat from the United Kingdom has been allowed to be imported into the United States by FSIS for human consumption since before the BSE epidemic occurred in the United Kingdom. The network of private veterinary practitioners that refers unusual cases to veterinary schools or State diagnostic laboratories around the United States provides an extensive surveillance system. FSIS performs both antemortem and post mortem inspections at all federally-inspected slaughter establishments, and inspectors condemn all animals with central nervous system disorders. State-inspected slaughter operations follow the same procedures.

USDA also maintains a database on these and other conditions. The Veterinary Diagnostic Laboratory Reporting System (VDLRS) is a database of selected disease conditions submitted by 29 State and university veterinary diagnostic laboratories throughout the United States, and includes the results of histologic examinations for BSE. The VDLRS is a cooperative effort of the American Association of Veterinary Laboratory Diagnosticians (AAVLD), the U.S. Animal Health Association (USAHA), APHIS' Veterinary Service Centers for Epidemiology and Animal Health, and the 29 laboratories mentioned previously.

c. *Public Health Service (PHS).* i. *CDC.* CDC conducts surveillance for CJD through examination of death certificate data compiled by the National Center for Health Statistics, CDC, for U.S. residents for whom CJD was listed as one of the multiple causes of death (Ref. 100). These data indicate that the annual CJD mortality rates in the United States between 1979 and 1993 have been relatively stable, ranging between only 0.8 case per million in both 1979 and 1990 and 1.1 cases per million in 1987. In addition, CJD deaths in persons younger than 30 years of age in the United States remain extremely rare (<5 cases per billion per year) (Ref. 101).

CDC is working with the Council of State and Territorial Epidemiologists to consider expansion of current CJD surveillance. CDC is also working with its four established Emerging Infections Programs (Minnesota, Oregon, Connecticut, and the San Francisco Bay area, California), the Georgia Department of Human Resources, and the Atlanta Metropolitan Active Surveillance Program to pilot enhanced surveillance efforts for CJD (Ref. 101). This effort includes an active search for v-CJD as described in the United Kingdom (Ref. 30). On August 9, 1996, the results of this enhanced CJD surveillance effort was published; no evidence of the occurrence of the newly described variant form of CJD was found in the United States. No evidence of v-CJD has been found in the United States.

ii. *National Institutes of Health (NIH).* A project of the Laboratory of Central Nervous System Studies of the National Institute of Neurological Diseases and Stroke is conducting investigations on slow, latent, and temperate viral infections associated with chronic degenerative neurological diseases. Important areas of study are the pathogenesis of slow infections and mechanisms of persistence in kuru and

CJD. Also intensive molecular, biological, genetic, and immunological studies are being conducted on amyloid formation in the brain in Alzheimer's disease, normal aging, Down's syndrome, and slow viral infections, and the elucidation of the de novo generation of infectious amyloid proteins from normal host precursor proteins in kuru, CJD, GSS syndrome, scrapie and BSE. Research on TSE's has also been conducted by the NIH Laboratory of Persistent Viral Disease. FDA maintains close contact with scientists in the laboratories and expects to use their expertise in the evaluation of inactivation methods and transmission studies.

iii. *Other actions.* On April 8, 1996, an interagency meeting at CDC including representatives from CDC, NIH, FDA, USDA, and the U.S. Department of Defense was held to disseminate conclusions from the WHO consultation regarding v-CJD and to coordinate preventive activities among these agencies to address the BSE and CJD issues.

2. International Actions

a. *United Kingdom.* Regulatory controls taken to manage the BSE epidemic in the United Kingdom and to address public health concerns include: (1) An action in June 1988 to make the disease reportable; (2) a ban in July 1988 on the feeding of ruminant-derived protein supplements to other ruminants; (3) an order in August 1988 for the compulsory slaughter and incineration of BSE suspect cattle; (4) a ban in November 1989 on the inclusion of specified bovine offal (brain, spinal cord, thymus, spleen, tonsils, and intestines) for human consumption; and (5) a ban in September 1990 on use of specified bovine offal in any animal feed.

A CJD Surveillance Unit was established to monitor CJD numbers in the United Kingdom. SEAC, consisting of experts in neurology, epidemiology, and microbiology from outside the British government, was established in 1990 to oversee all aspects of TSE's and human and animal health. USDA has a representative on this committee.

Major regulatory actions occurring after the SEAC report on nv-CJD (Ref. 90) include legislation to ban the feeding of mammalian meat and bone meal to any farmed animal, and legislation to ban the use of cattle head meat for human consumption.

b. *WHO.* WHO has held meetings on the spongiform encephalopathies in 1991, 1993, 1995, and 1996, and a meeting in collaboration with the Office International des Epizooties (OIE) in 1994. The general purposes of these meetings were to review the existing state of knowledge on spongiform encephalopathies including BSE, to evaluate possible means of transmission, and to identify risk factors for infection. A specific purpose was to review the possible human public health implications of animal spongiform encephalopathies, with special emphasis on BSE. The group of international experts convened in April 1996 by WHO recommended that all countries should ban the use of ruminant tissues in ruminant feed. The WHO group also declared that milk and milk products, including such products from the United Kingdom, are safe for human consumption and that gelatin in the food chain is considered safe because its preparation effectively destroys BSE. Finally, the group concluded that tallow could be safe if effective rendering procedures are in place (i.e., rendered as protein-free) (Ref. 2).

c. *OIE.* OIE has supported the U.K. ban on the use of specified offals and has recommended that the same action be taken in other countries with a high incidence of the disease (Ref. 102). OIE has held meetings in 1990, 1991, 1992, 1995, and 1996, and has developed guidelines concerning animals and animal products to prevent movement to unaffected countries.

d. *European Community (EC).* The EC has held a series of meetings related to BSE. Following issuance of the U.K. SEAC statement suggesting a possible link between nv-CJD and BSE, the EC imposed a ban on British cattle, beef and bovine derivatives (Ref. 103).

3. Voluntary Measures by the U.S. Animal Industries

a. *Voluntary ban on rendering adult sheep.* In 1989, the National Renderers Association (NRA) and the Animal Protein Producers Industry (APPI) recommended to their members that they stop rendering adult sheep or providing sheep offal for sale as meat and bone meal for inclusion in cattle feed (Ref. 104). Following the recommendation of the voluntary ban, FDA carried out a survey of current practices in the United States for rendering or otherwise disposing of adult sheep carcasses and parts, specifically head, brain, and spinal cord. Limited inspections of rendering plants were conducted in 1992 to: (1) Assess compliance by U.S. renderers with the voluntary ban; (2) identify rendering plant practices concerning adult sheep; and (3) determine if rendered adult sheep protein byproducts were being sold or labeled for use as feed or feed components for cattle. Of the 19 plants surveyed, 15 rendered carcasses or offal of adult sheep. These 15 plants processed more than 85 percent of the adult sheep rendered in the United States. Eleven of the 15 plants rendered carcasses of adult sheep with heads, 7 of the 15 rendered sheep carcasses separately from other species, 6 of the 15 maintained meat and bone meal from adult sheep separate from meat and bone meal from other species, and 4 of the 15 rendered sheep that had died of causes other than slaughter. Six of the 11 renderers processing adult sheep with heads had sold meat and bone meal to manufacturers of cattle feed. Thus, the rendering industry's voluntary ban on the rendering of adult sheep or providing sheep offal for use in cattle feed was not fully implemented at the time of the survey (Ref. 105).

b. *Voluntary ban on feeding ruminant proteins to ruminants.* On March 29, 1996, the National Cattlemen's Beef Association (NCBA), the National Milk Producers Federation, the American Sheep Association, the American Veterinary Medical Association, the American Association of Veterinary Medical Colleges, and the American Association of Bovine Practitioners announced the recommendation of a voluntary ban on the feeding of ruminant-derived proteins to ruminant animals (Ref. 106). USDA, PHS, the American Society of Animal Science, and other organizations announced support for the voluntary ban (Refs. 107 and 108). According to the NCBA (Ref. 109), a comprehensive communication strategy, seeking removal of ruminant-derived proteins from the rations of ruminants, was implemented in May 1996 by the feed industry, nutritionists, veterinarians, extension specialists, and dairy and beef producers. NCBA has not conducted a survey to assess the impact of its communication strategy; however, NCBA did point out that past requests for voluntary action by the cattle industry have been quite successful, approaching 90 percent compliance. In contrast, an anonymous comment to the ANPRM suggested a compliance level of less than 5 percent (Ref. 110). FDA has not conducted a survey to ascertain the level of compliance with the voluntary ban.

G. Processing Animal Tissues for Feed Ingredients

1. Current Rendering Practices

The following discussion on current rendering practices comes directly from comments supplied to FDA in response to the ANPRM from representatives of

APPI and NRA. Knowledge about the four basic types of rendering systems that are most commonly used in the United States today may be crucial in dealing with the TSE issue in this country. Data on the inactivation of the BSE and scrapie agents following simulation of the most commonly used basic types of rendering systems in the United States could be quite useful, especially because some of these systems do not appear to have been used in the only published rendering study on BSE inactivation (Ref. 85).

Rendering, the process of cooking raw material to remove the moisture and fat from the solid protein portion of animal tissues, has been practiced by humans for more than 2,000 years. The United States rendering industry has developed over the last 160 years. Modern rendering systems are high-technology recycling processes that efficiently convert animal byproducts (shop fat and bone, beef and pork slaughterhouse materials, poultry offal, fish, etc.) to stable protein and fat supplements for feed.

Current technology consists of four basic types of rendering systems—batch cooker, continuous cooker, continuous multi-stage evaporator, and continuous preheat/press/evaporator. All systems consist of three basic steps: Grinding the raw material, cooking it to remove moisture, and separating the melted fat from the protein solids.

Batch cookers are multiple units, each consisting of a horizontal, steam-jacketed cylindrical vessel with an agitator. Batch cookers are operated at atmospheric pressure. The cooked material is discharged to the percolator drain pan, which contains a perforated screen that allows the free-run fat to drain and be separated from the protein solids known as ''tankage.''

Because ''tankage'' contains considerable fat, it is processed through a screw press to complete the separation of fat from solids. The fat discharged from the screw press usually contains fine solid particles that are removed by either centrifuging or filtration. The protein solids discharged from the screw press are known as ''cracklings,'' which normally are screened and ground with a hammer mill to produce protein meal.

The continuous cooker rendering system normally consists of a single continuous cooker, operating at atmospheric pressure. The discharge from the continuous cooker usually passes across either a vibrating screen or stationary perforated screen to allow the free-run fat to drain. The subsequent steps in the continuous cooker rendering process are similar to those described before for the batch cooker.

In the continuous multi-stage evaporator rendering system, crushing is used as the first stage of size reduction of the raw material. A fat recycle stream is then used to deliver the material as a pumpable slurry through the secondary grinding step to reduce further the particle size. Particle size and fat ratios are important components of this system. The slurry discharge from the final stage of evaporation is pumped to a centrifuge which removes most of the fat and part of it is recycled back to the second stage of size reduction. The solids discharged from the centrifuge are conveyed to screw presses which complete the separation of fat from the protein solids.

The continuous preheat/press/evaporator rendering system is known by a variety of names including the Stord dewatering rendering system and the Atlas low temperature wet rendering system. In either case, raw material is ground in two stages and passes through the preheater to raise the temperature to 180 to 190 °EF before entry to the twin screw press. The press separates this material into two phases: A presscake of solids containing moisture and a low fat concentration, and a liquid containing mostly water (stickwater) with fine solids, soluble protein, insoluble protein and melted fat.

The press liquid is processed either by passing through a multistage evaporator system to remove the water before centrifuging to remove the fine solids from the fat, or by passing through a centrifuge to separate the fat before multistage evaporation of the remaining water/fine solids fraction. The liquid separation system consisting of two stages of centrifuges completes the separation of the melted fat from the solids and water. In this system, the screw press normally used to process the ''tankage'' is no longer needed. Longer drying times are needed with this system as compared to previous systems because of the early fat removal (less fat means less effective heat transfer).

The agency encourages further research into methods of deactivation of the BSE agent during the rendering process.

2. Assay Methodologies for Proteins

Enforcement of the proposed regulation would be facilitated if a test to detect and distinguish ruminant from nonruminant materials in feeds or feed ingredients was available. However, practical assays that could be used to enforce the proposed regulation are not available at this time. The test procedure would need to exhibit a high degree of sensitivity and selectivity; that is, the test must be able to detect the analyte of interest to the exclusion of other components. A test for acceptable rendered products in animal feed must therefore be able to discriminate and differentiate between permitted and prohibited animal derived proteins. Other factors of importance are the ruggedness of the test method, speed, and simplicity of design.

An enzyme-linked immunosorbant assay (ELISA) based analytic method that is both sensitive (detects low levels of analyte) and specific (detects primarily the analyte of interest) is one possibility. ELISA is a relatively straightforward methodology. There are numerous commercial sources for antisera capable of binding to bovine, ovine, porcine, and caprine proteins. Antisera have also been generated from muscle extracts and validated for use in USDA-approved ELISA methods to determine the identity of raw and cooked meats (Refs. 111 and 112). However, rendered products present a unique problem because rendering causes the destruction of most of the antibody binding epitopes needed for an ELISA test. Therefore, detection of rendered proteins by a given antibody cannot be automatically assumed.

Other potential methodologies include western blot analysis, capillary electrophoresis, and high pressure liquid chromatography. The applicability of these three methods to this issue has not been addressed. Furthermore, they require expensive, specialized equipment and a high degree of technical competence.

The agency encourages research to detect and distinguish ruminant from nonruminant materials in rendered products and animal feeds.

III. Statutory Provisions Regarding Food Additives

The term ''food'' as defined in the act includes animal feed. Section 201(f) of the act (21 U.S.C. 321(f)) defines food as ''articles used for food or drink for man or other animals'' and ''articles used for components of any such article.'' Furthermore, any substance whose intended use results or may reasonably be expected to result in its becoming a component of food is a food additive unless, among other things, it is GRAS or is the subject of a prior sanction. Section 402(a)(2)(C) of the act (21 U.S.C. 342(a)(2)(C)) deems food adulterated ''if it is, or it bears or contains, any food additive which is unsafe within the meaning of section 409 * * *.'' Under section 409(a) of the act (21 U.S.C 348(a)), a food additive is unsafe unless

a food additive regulation or an exemption is in effect with respect to its use or its intended use.

A food additive regulation is established by the submission and approval of a food additive petition, as provided in 21 CFR 571.1, or on FDA's initiative as provided in 21 CFR 570.15. FDA on its own initiative or at the request of an interested party, also may propose to determine that a substance intended for use in animal feed is not GRAS and is a food additive subject to section 409 of the act as provided in § 570.38 (21 CFR 570.38). Subsequent to the publication of such a proposal and after consideration of public comments, FDA may issue a final rule declaring the substance to be a food additive and require discontinuation of its use except when used in compliance with a food additive regulation.

A. GRAS Determination

A determination that a substance added directly or indirectly to a food is GRAS, is generally based on specific information regarding the composition of the substance, its use, method of preparation, methods for detecting its presence in food, and information about its functionality in food (21 CFR 570.35) as determined by experts qualified by scientific training and experience to evaluate the safety of such a substance. A substance added to food becomes GRAS as the result of a common understanding about the substance throughout the scientific community familiar with safety of such substances. The basis of expert views may be either scientific procedures, or, in the case of a substance used in food prior to January 1, 1958, experience based on common use in food (§ 570.30(a)) (21 CFR 570.30(a)). General recognition of safety through experience based on common use in food prior to January 1, 1958, may be determined without the quantity or quality of scientific studies required for the approval of a food additive regulation. However, substances that are GRAS based on such use must be currently recognized as safe based on their pre-1958 use. (See *United States* v. *Naremco,* 553 F.2d 1138 (8th Cir. 1977); compare *United States* v. *Western Serum,* 666 F.2d 335 (9th Cir. 1982).) A recognition of safety through common use is ordinarily to be based on generally available data and information (§ 570.30(c)). An ingredient that was not in common use in food prior to January 1, 1958, may achieve general recognition of safety only through scientific procedures.

General recognition of safety based upon scientific procedures requires the same quantity and quality of scientific evidence as is required to obtain approval of a food additive regulation for the ingredient (§ 570.30(b)). (See *United States* v. *Naremco,* 553 F.2d at 1143.) A substance is not GRAS if there is a genuine dispute among experts as to its recognition (*An Article of Drug * * * Furestrol Vaginal Suppositories,* 251 F. Supp. 1307 (N.D. Ga. 1968), *aff'd* 415 F.2d 390 (5th Cir. 1969).) Further, general recognition of safety through scientific procedures must be based upon published studies (*United States* v. *Articles of Food and Drug Colitrol 80 Medicated,* 372 F. Supp. 915 (N.D. Ga. 1974), *aff'd,* 518 F.2d 743, 747 (5th Cir. 1975)), so that the results are generally available to experts. It is not enough, in attempting to establish that a substance is GRAS, to establish that there is an absence of scientific studies that demonstrate the substance to be unsafe; there must be studies that show the substance to be safe (*United States* v. *An Article of Food * * * Co Co Rico, supra.*)

Conversely, a substance may be ineligible for GRAS status if studies show that the substance is, or may be, unsafe. This is true whether the studies are published or unpublished (50 FR 27294 at 27296, July 2, 1985). If there are studies that tend to support a finding that a particular substance is GRAS, but also studies that tend to support a contrary position, the conflict in the studies, just as a conflict in expert opinion, may prevent the general recognition of the safe use of the substance.

B. Prior Sanction

Under section 201(s) of the act, the term ''food additive'' does not apply to any substance used in accordance with a sanction or approval granted prior to enactment of section 201(s) of the act and granted under the act, the Poultry Products Inspection Act (21 U.S.C. 451 *et seq.*), or the Federal Meat Inspection Act (21 U.S.C. 601 *et seq.*). Section 570.38(d) provides that if the Commissioner of Food and Drugs is aware of any prior sanction for use of a substance, he will, concurrently with a notice determining that a substance is not GRAS and is a food additive subject to section 409 of the act, propose a separate regulation covering such use of the substance.

In the case of the materials subject to this proposed rule, FDA has determined that it is unaware of any applicable prior sanction. Any person who intends to assert or rely on such sanction is required to submit proof of the existence of the applicable prior sanction. The failure of any person to come forward with proof of such an applicable prior sanction in response to this notice will constitute a waiver of the right to assert or rely on such sanction at any later time.

C. Food Additive Status of Ruminant Tissues

The agency recognizes that processed ruminant byproducts have a long history of use in animal feeds without known adverse effects. However, the evidence as discussed in sections I and II.A. through II.D. of this document, for the development of a new pattern of disease transmission, now indicates that these ingredients can no longer be categorically regarded as safe. The agency tentatively concludes that, based on this evidence, use of such products in ruminant feed is not GRAS. The agency is proposing this regulation in light of the findings and conclusions described in sections I and II in this notice. Nor is the agency aware of a prior sanction for any feed products that contain these tissues. Therefore, FDA is proposing that the addition of protein derived from ruminant tissues to ruminant feed would constitute the use of an unapproved food additive because no regulation is in effect providing for such use. Any ruminant feed that contains protein derived from ruminant and mink tissues would be adulterated. Accordingly, FDA is proposing to list protein derived from ruminant tissues in part 589.

IV. Comments

FDA's May 1996 ANPRM requested public comment and information on all aspects of TSE's, including BSE, and the potential consequences of a prohibition on the feeding of ruminant protein to ruminants. The agency received nearly 600 comments, including many that were submitted long after the comment period ended. The agency has attempted to address the comments in this proposal. If there are any significant concerns that the agency has not addressed, these concerns should be brought to the agency's attention in timely comments on this proposal. Comments that were specific to the topics covered by the other sections of this preamble were considered in the preamble as written. Comments are discussed in the text of some of these sections. The following is a general discussion of the comments received.

Many comments, especially from renderers, meat packers, feed companies and farmers, opposed the prohibition of ruminant protein being fed to ruminants. The main reasons offered were the lack of evidence of BSE in the United States, lack of scientific data to support the proposal in the absence of

BSE, environmental concerns, lack of an assay or other practical means to support enforcement, and the economic hardship that would fall upon the animal producers, slaughter facilities, renderers, feed manufacturers, and packers. Support for such a prohibition from consumer groups, pharmaceutical firms, scientists and veterinarians, and some livestock organizations, emphasized a potential effect on human health, the experience and data from the United Kingdom, and significant economic detriment if a BSE epidemic were to occur in this country. Other comments described a need to ensure that exported U.S. bovine-derived products met international standards and guidelines, and to maintain consumer confidence in the beef and dairy industries even though those comments acknowledged that there is a minimal potential risk of infectivity to animals and humans.

The agency requested scientific information regarding the occurrence, transmission, etiology, pathogenesis, epidemiology, and inactivation of TSE agents. Many comments were received that contained useful scientific information that was considered in the preparation of this proposed rule, as described in this preamble and supporting documents.

Three comments suggested that the documented existence of nonBSE TSE's, and the presence of ''downer'' cows (cows unable to walk) in the United States is evidence that BSE is present in this country. Three comments stated that the BSE surveillance in the United States provides sufficient assurance that BSE does not exist in this country. A number of persons commented on whether specific tissues, such as milk, blood, and gelatin, should be excluded from any prohibition, with nearly all supporting such exclusion.

The agency requested information on the economic impact of the described action. Numerous comments provided data on volume of product impacted, potential economic benefits, and cost of compliance to affected persons. The data were used to develop the preliminary economic assessment supporting this proposed rule.

The agency requested information on the environmental impact and potential mitigating factors of the described action. Many comments stated that alternative disposal of the prohibited carcasses would be less environmentally safe than rendering. These and other comments were considered in the development of the environmental assessment.

Numerous comments were received regarding the need to prohibit only tissues that have been demonstrated to be infective. Generally, the comments stated that tissues that have been proven to be noninfective should be exempted. Although the agency is proposing a rule that would prohibit the use of all ruminant-derived protein in ruminant feeds, the agency will, as explained elsewhere in this document, consider a partial ruminant-to-ruminant prohibition as well as a mammalian-to-ruminant prohibition.

Many comments supported establishment of Hazard Analysis Critical Control Points (HACCP) for the rendering industry, often with concurrent support for current good manufacturing practices (CGMP's) for animal-derived proteins. For example, the American Feed Industry Association proposed a specific set of Good Manufacturing Practices for the producers of animal protein products, and the National Renderers Association proposed a specific HACCP regulation for rendering operations. The agency agrees that the need for HACCP, perhaps supported by CGMP's, for animal-derived proteins could be considered in future rulemaking. Several comments were received regarding labeling requirements for animal-derived proteins. The majority of the comments supported a statement of the origin of animal-derived protein. The agency has included a labeling requirement in the proposed rule.

V. Analysis of Alternatives

A. Overview

In addition to the proposed ruminant-to-ruminant rule, the agency is considering alternative approaches. The alternatives include: (1) excluding from ruminant feed all ruminant and mink materials except those that have not been found to present a risk of transmitting spongiform encephalopathy (partial ruminant-to-ruminant prohibition); (2) prohibiting the use in ruminant feed of all mammalian protein (mammalian-to-ruminant prohibition); (3) prohibiting the feeding of materials from species in which TSE's have been diagnosed in the United States (sheep, goats, mink, deer, and elk); (4) prohibiting the feeding of specified sheep and goat offal, as proposed by the agency in 1994; (5) other alternatives that might be proposed by the comments; and (6) no action.

Analysis of the advantages and disadvantages of the options follows. Analysis of costs and benefits, including detailed economic analysis, also appears in section IX. of this document. Environmental consequences are discussed in section VIII. of this document.

In determining the scope of the final rule, the agency will weigh carefully the comments received, along with material contained in the administrative record for this proposal and the comments submitted in response to the ANPRM. Comments regarding the scope of the rule, including those comments supporting other options other than the proposed option, should be addressed accordingly.

B. Ruminant-to-Ruminant Prohibition

Advantages of this option, compared with the ''no action'' option, are discussed in detail in section I. of this document. The advantages of this option that are discussed in that section would apply if BSE were to occur in this country. As discussed in separate sections that follow, there would also be environmental and economic advantages to the ruminant-to-ruminant option, if BSE were to occur in this country. Disadvantages of the ruminant-to-ruminant option, compared to the ''no action'' option, would be relevant primarily if BSE did not occur in the United States. These disadvantages would include the time and expense required to comply with the provisions of the regulation, and the limited, short term environmental effects described in section VIII. of this document.

Compared with the mammalian-to-ruminant option, the ruminant-to-ruminant option has the advantages of being tailored more precisely to the identified scientific concerns, and less burdensome on the affected industries. Economic and environmental costs would be less. The major disadvantage is that the ruminant-to-ruminant option results in more complexity for the regulated industries, and thereby provides less assurance of compliance. This is explained further in the discussion of the mammalian-to-ruminant option, in section V.D. of this document.

Compared to the other remaining options, which are less restrictive, the ruminant-to-ruminant option provides greater assurance of protection of the public health and, if BSE were to occur in the United States, lower economic and environmental costs. The disadvantages relate generally to the greater economic and environmental costs that would be incurred if BSE did not occur in the United States.

C. Partial Ruminant-to-Ruminant Prohibition

As an alternative to the proposed ruminant-to-ruminant prohibition, the agency is considering a partial

ruminant-to-ruminant prohibition which would exclude from ruminant feed all ruminant and mink materials except those that have not been found to present a risk of transmitting spongiform encephalopathy. The exclusions would be in addition to milk products, gelatin and bovine blood, which are excluded in the proposed rule. Possible exclusions include slaughter byproducts from bovine that have been inspected and passed in inspected slaughter facilities, except the brain, eyes, spinal cord, and distal ileum. The four named tissues would be prohibited because they have been shown through experimental trials and bioassays to transmit spongiform encephalopathy. The remaining tissues have not been demonstrated to transmit spongiform encephalopathy.

This option has the advantage of having its prohibitions based primarily on scientific information related to infectivity of specific tissues. A number of persons who commented on the ANPRM urged the agency to base its regulation entirely on such scientific information. In addition, this option would likely involve lower lost sales revenues to the affected industries, and could have fewer adverse economic effects, than would the other options.

However, the agency has three concerns with regard to the adequacy of this option in providing sufficient protection for the public health. First, FDA recognizes that it may be impractical in the slaughter and rendering processes to segregate and exclude the bovine tissues that have not been found to present a risk. For example, USDA has expressed reservations that separating the distal ileum from the other intestinal offal could jeopardize a slaughter plant's ability to meet pathogen reduction goals required under USDA's HACCP regulations. Furthermore, regulatory enforcement of a prohibition affecting only specified bovine tissues may be impractical in the absence of specific diagnostic methods for identifying protein derived from such tissues. If a partial prohibition were adopted, it would be based on a finding that practical methods can be implemented for segregating, processing, storing, and identifying feed materials derived from tissues that have not been found to present a risk.

Second, this option would be inconsistent with actions taken in a number of other nations. For example, CDC has commented that any prohibition of lesser scope than a ruminant-to-ruminant prohibition would place the United States out of step with the international public health community.

Third, limiting the prohibition of tissues to those that have been shown to be infective would not address the risk that may be presented by other tissues. Definitive assays using methods more sensitive than currently available methods might identify such additional tissues as infective. The possibility of undetected low dose exposure cannot be eliminated, particularly for tissues such as lymph nodes and spleens which would be expected to be infective (Ref. 1).

These issues raise a substantial question as to whether the tissues could be GRAS. To achieve the highest level of public health protection, the agency believes that it may be reasonable to assume that, in the absence of scientific data definitively establishing that each tissue does not transmit spongiform encephalopathy, all ruminant tissues present a risk of infectivity.

The agency nevertheless welcomes comments on this alternative to the proposed ruminant-to-ruminant prohibition and especially invites comments on possible practical means of separating the distal ileum in compliance with USDA and industry standards, as well as the practicality of the removal of brain, spinal cord, and eye and the segregation of these tissues from others in the slaughter plant.

D. Mammal-to-Ruminant Prohibition

The agency received comments in support of a rule that would prohibit the use in ruminant feed of all mammalian-derived protein. For instance, the American Feed Industry Association, NRA, and APPI expressed concerns that segregating certain mammalian derived proteins from others would not be feasible because of regular commingling of protein products at feed mills and rendering facilities. A mammalian-to-ruminant prohibition would provide greater assurance of industry compliance than either a partial or total ruminant-to-ruminant prohibition because practical analytical methods exist for distinguishing mammalian from nonmammalian proteins. Implementation of a mammal-to-ruminant prohibition by the regulated industries would be less complex, and would reduce the potential for contamination of cattle feeds with material intended for feeding monogastric animals. Contamination of cattle feeds with material intended for feeding nonruminants was the primary reason that the United Kingdom has prohibited mammalian proteins in the rations of cattle. A mammal-to-ruminant prohibition would enable the continued use of Association of American Feed Control Officials definitions for the purpose of identifying and labeling products covered by the prohibition, and would not require additional or new labeling. Finally, concerns were expressed that allowing certain products containing meat and bone meal to be used in ruminant feeds while prohibiting others would lead to instability in financially sensitive commodity markets for animal protein.

On the other hand, the agency is not aware of any scientific data that establish or suggest TSE infectivity in nonruminant mammals except in mink. Thus, excluding nonruminant tissues from ruminant feed would be based primarily on the view that the possibility of infection of nonruminant tissue through cross-contamination or commingling with ruminant tissue is sufficient to preclude GRAS status for the nonruminant tissue. However, FDA is aware that some portions of the affected industries would prefer to segregate ruminant from nonruminant tissues, and believe that such separation is practical. Accordingly, the agency invites comments on the relative merits and disadvantages of a mammal-to-ruminant prohibition compared with a total or partial ruminant-to-ruminant prohibition.

E. Prohibition of Materials From U.S. Species Diagnosed With TSE's (Sheep, Goats, Mink, Deer, and Elk)

This option would involve requiring that ruminants not be fed any proteins derived from any U.S. animal species in which a TSE has been diagnosed. This includes sheep, goats, mink, deer, and elk. This approach would eliminate the scrapie agent, along with TME and CWD, from ruminant feed, and thereby reduce the risk of BSE in cattle caused by TSE transmission from other species. However, it would not prevent the spread of BSE among cattle if BSE occurred for some other reasons, e.g., by a spontaneous mutation in cattle or importation of animals with BSE, and the animals were processed and subsequently included in ruminant feed. As explained in section IX. of this document, this option involves lower economic costs than the three options previously described, in the absence of a BSE outbreak.

F. Sheep-Specified Offal Prohibition

The option of prohibiting only protein from specified offal from sheep and goats for use in ruminant feed would eliminate the scrapie agent from bovine feed. However, it would not prevent the spread of BSE among cattle if BSE occurred for some other reason, e.g., by

a spontaneous mutation in cattle or importation of animals with BSE, and the animals were processed and subsequently included in ruminant feed. The agency notes that if it were to select this option, it would reconsider its statement in the 1994 proposed rule that sheep less than 12 months of age presented a minimal risk. Cases of scrapie in sheep as young as 7 months have been reported (Ref. 113). Although the risk presented by young animals may be minimal, excluding them may provide inadequate protection to the public health. As explained in section IX. of this document, this option involves lower economic costs than the options described previously, in the absence of a BSE outbreak.

G. No Action

The advantages and disadvantages of this option, in relation to the other options, are discussed in detail in section I. of this document and in the preceding subsections of this section, as well as the environmental and economic sections. In general, this option offers lower economic and environmental costs if BSE does not occur in the United States, and higher such costs (in addition to public health implications) if BSE does occur.

VI. Description of the Proposed Rule

A. Introduction

1. Regulatory Alternatives

Typically, FDA regulates products that are of public health concern through a combination of regulatory tools including: labeling for appropriate use; CGMP regulations and, recently, HACCP regulations; specifications for the product or its manufacture; and testing to determine the presence or level of the agent of concern. Use of two or more of these means provides for appropriate reinforcement to ensure that the public is protected.

The agency's choice of readily available approaches for regulating animal protein products derived from ruminant and mink tissues is limited. For example, there are no practical tests for the presence of the TSE agent or of ruminant protein in animal feed. No commercial method of deactivating the TSE agent in animal protein products has been scientifically validated as effective. None of the agency's CGMP or HACCP regulations apply to this situation. Labeling requirements can be used but, by themselves, do not meet the agency's regulatory objectives.

2. The Regulated Industry

Often, the industry that manufactures and distributes an FDA-regulated product is fairly easily characterized. This facilitates regulation. That is not the case for animal protein products, as the following brief overview makes clear.

Renderers collect animal tissues from a variety of sources, and process these tissues into both protein and nonprotein products. The renderers may be specialized (packer/renderer) or independent. The packer/renderer, which involves a renderer associated with a large slaughter operation, specializes in one species—primarily cattle, swine, or poultry. Thus, whether the packer/renderer handles ruminant materials is fairly easily determined. The independent renderer, on the other hand, obtains a variety of raw materials ranging from restaurant scraps to byproducts from multi-species slaughtering operations to dead animals obtained from farmers. Typically, the independent renderer does not have a practical method to separate incoming ruminant from nonruminant materials, and thus commingles both ruminant and nonruminant materials in the rendering process. The rendered product is typically designated ''meat and bone meal,'' but rendering operations produce a variety of other products. Renderers sell their products to animal protein blenders, animal feed manufacturers or pet food manufacturers. Virtually all rendered material at present is used ultimately for pet food or the feed of livestock or poultry.

Animal protein blenders mix animal and plant protein materials to meet a protein guarantee stated on the label, and to make a balanced nutritional product. Typically, the blender does not separate ruminant from nonruminant animal protein in its blending operation, although it may keep mammalian, poultry, fish and soybean meal protein separate at least in the initial stages. The blender sells its products to feed or pet food manufacturers. Some renderers also blend animal protein products.

Feed manufacturers use the protein material to make a complete feed (ready to be feed to animals), or a concentrated feed that needs to be further diluted (blended) before it can be fed to animals. The feed may be manufactured by an off-farm miller, or on the farm. Feed that is manufactured off-farm may be sold to one or more persons (for blending and/or further distribution) before reaching the farm.

Farmers that feed animals typically raise one species, but may have more than one (including both ruminants and nonruminants). Only about 10 percent of all animal protein products are fed to ruminants (mainly cattle) but approximately half of all animal protein products comes from ruminants.

3. Enforcement Considerations

The industry scenario described in the preceding section presents unique enforcement challenges. The agency is aware, from the comments to the ANPRM and other sources, of concerns that the regulatory impact be minimized. The agency is also aware of the need to provide incentive for innovation, e.g., in testing methodology and manufacturing technology, that would reduce the need for regulation. Finally, the agency is aware of the need, in designing a regulatory program, to acknowledge the different circumstances that exist in the industries previously described.

Therefore, the agency has designed a proposed regulatory scheme using the following principles. First, the agency has identified minimally necessary requirements to meet its regulatory objectives. The agency's goal is to apply risk management principles that minimize risk. Second, the proposed regulation applies greater restriction where the risk is greater—for example, where a firm handles both ruminant and nonruminant materials and intends to keep them separated. Third, the agency intends to rely on normal business records for much of the documentation it needs.

A fourth and most important principle concerns the related objectives of flexibility and providing incentives to reduce recordkeeping and labeling requirements. The proposed regulation provides for the reduction or elimination of recordkeeping and labeling requirements, upon the development of methods for detection, deactivation, or verification of product identity. These provisions are described further in the discussion that follows.

Industry-wide adoption of scientific advances including, or in addition to, those specified in the regulation, could ultimately lead to amendment or revocation of any final regulation. An example of an additional method would be the development of a practical method to detect the presence of ruminant protein in animal protein products or feed, which could be used for quality control by firms that separate ruminant from nonruminant protein, and by firms downstream from renderers.

Similarly, research leading to identification of the TSE causative agent and the etiology of BSE, and the characterization of the zoonotic nature of animal TSE's, could also lead to amendment or revocation of any final regulation.

The agency has tentatively decided not to place any record keeping, labeling or other specific requirement on firms that handle only protein materials from nonruminant sources. An example would be a rendering operation that is part of a swine slaughter operation. However, if these firms would use or intend to use animal protein products containing ruminant tissues in ruminant feed, or caused such use or intended use, the feed would be adulterated under the act.

The agency has also tentatively decided to require farmers (those responsible for feeding ruminant animals) only to make available copies of invoices and labeling for feed purchases. Farmers would not be required to maintain written procedures for handling animal protein products. These minimal requirements would apply even if the farmers were feeding both ruminant and nonruminant animals. Purchase records would be used primarily for traceback purposes. Because only minimal requirements would be placed on farmers, the proposed rules require that labeling for the animal protein and feed products caution against feeding the products to ruminants. Comments on these two tentative decisions are encouraged.

B. Outline of the Proposed Regulation

The proposed regulation places two general requirements on persons that manufacture, blend, process, and distribute animal protein products and feeds made from such products. The first requirement is to place cautionary labeling on the protein and feed products. The second is a requirement to provide FDA with access to sales and purchase invoices, for compliance purposes. For example, an invoice obtained from a feed manufacturer for a protein product not labeled with the cautionary statement could be used to trace back to the supplying renderer to ensure that it manufactures and distributes animal protein product from nonruminant sources.

Firms (renderers, blenders, and feed manufacturers and distributors) that handle animal protein products from both ruminant and nonruminant sources, and that intend to keep the products separate, would have certain additional requirements related to their source of nonruminant material; the need for separate facilities or cleanout procedures; and the need for SOP's. The same requirements would apply to firms that handle feeds containing animal protein products from both ruminant and nonruminant sources, and that intend to keep the feeds separate. Requirements would be greater for these operations because of the greater risk they would present for the possibility of ruminant protein being fed to ruminants.

The proposed rule provides that some or all of the regulatory requirements would not apply if innovations such as development of test methods and deactivation processes for TSE agents were scientifically validated and put into commercial use. Provisions for use of such methods do not imply that the agency believes that such agents are or will be in the animal protein products. The objective is to minimize the risk that the agent would occur in the products, regardless of the level of risk. Certain minimal but additional requirements would be imposed in such circumstances. For example, because the innovations likely would be applied by renderers, the renderers would need to certify to downstream customers that the methods were being utilized.

Section 589.2000(a) presents definitions of certain words used in the regulation. The definition of ''protein derived from ruminant and mink tissues'' excludes blood from bovines, milk proteins, and gelatins. Thus, those products are not subject to the regulatory provisions of the regulation. The proposed rule does not apply to any nonprotein animal tissues such as tallow or other fats. ''Renderer'' includes firms, not traditionally considered to be included within the definition of that term, but that collect animal tissues from various sources and subject them to minimal processing before offering the materials for use in animal feed. Also, ''feed manufacturers'' is defined to include both off-farm and on-farm feed manufacturing operations.

Section 589.2000(b) declares that protein derived from ruminant and mink tissues is not GRAS when intended for use in the feed of ruminant animals. The use or intended use of such material in ruminant animal feed causes the feed to be adulterated.

Section 589.2000(c) establishes regulatory requirements for renderers that manufacture products that contain or may contain protein derived from ruminant and mink tissues. (''May contain'' allows for the fact that the renderer may not be able to determine the species of some incoming material). These renderers typically process both ruminant and nonruminant materials, but do not attempt to separate ruminant from nonruminant materials. Section 589.2000(e) covers renderers that intend to separate such materials. As mentioned, renderers that process exclusively nonruminant materials are not covered by the specific requirements of the regulation. Section 589.2000(c) applies to animal protein products intended for use in animal feeds, as well as animal feeds containing such products.

Two requirements would be placed on renderers covered by § 589.2000(c). First, they would be required to label their products to indicate that they contain (or may contain) protein derived from ruminant and mink tissues, and that the materials should not be fed to ruminant animals or used to manufacture feed for ruminants. Second, the renderers would be required to maintain copies of sales invoices for all their animal protein products, and to make those copies readily available for inspection. As an example, FDA would use the invoices to follow up with customers to verify that the customers are not using the products to manufacture ruminant feed. Because sales invoices are normal business records, the agency believes that the additional burden imposed by this requirement would be minimal.

Section 589.2000(c) renderers would be exempted from the labeling and record requirements if they used a manufacturing method that deactivates the agent that causes TSE's, or a test method that detects the presence of the agent that causes TSE's. Both methods would have to be validated by FDA, and made available to the public. The regulation would require ''routine'' use. That is, renderers would be required to use the test method on all incoming material or in each batch it manufactures.

Section 589.2000(c) renderers would be exempted from the record requirements (but not the labeling requirement) if they used a safe method to mark the presence of the materials. The marking could be visible to the naked eye, e.g., through use of a dye, or by a nonvisual means. One ANPRM comment recommended use of a colored uniform fine iron product to identify specific feed ingredients. If the marking is not visible, the marking agent must be detectable by a method that has been validated by FDA, and made available to the public. The mark must be permanent, i.e., it must be visible in mixed feed as used on the farm.

Section 589.2000(d) establishes regulatory requirements for persons other than renderers and persons responsible for feeding ruminants that handle animal protein products or feeds containing such products. This includes protein blenders, and feed manufacturers and distributors. However, as in the case of renderers, those firms that would otherwise be included in § 589.2000(d) but that handle both ruminant and nonruminant

materials and intend to separate the materials would be covered by § 589.2000(e) instead. Protein blenders, and feed manufacturers and distributors, that handle only nonruminant materials are excluded from the regulatory requirements of the proposed rule.

Persons covered by § 589.2000(d) would be subject to the same requirements as renderers, i.e., labeling and records. The records would include invoices both to cover purchases and sales of animal protein products and feeds containing those products. For on-farm mixers, production records could be substituted for sales invoices.

Section 589.2000(d) firms would be exempt from the labeling and record requirements if they purchased materials from renderers that certified the use of deactivation or detection methods as described in § 589.2000(c). They would also be exempt from the labeling and record requirements if they purchased materials from persons other than renderers who certified that they purchased materials from renderers who certified the use of deactivation and detection methods as described in § 589.2000(c). Paragraph (d) firms would also be exempt if they used the deactivation or detection methods described in § 589.2000(c), where use of such method is appropriate for the particular firm.

Paragraph (d) firms would be exempt from the record requirements if they purchased visibly-marked materials, or purchased from renderers that certified the use of marking methods as described in § 589.2000(c). They would also be exempt from the record requirements if they used the marking methods as described in § 589.2000(c).

Section 589.2000(e) establishes regulatory requirements for renderers, protein blenders, feed manufacturers and distributors, and independent haulers that handle both ruminant and nonruminant materials, and intend to keep the products separate. Section 589.2000(e) establishes four kinds of requirements. First, the firms would have the same labeling and recordkeeping requirements as specified in paragraphs (c) and (d) of § 589.2000, except that the labeling requirement would apply only to the ruminant and mink materials. Second, a renderer's source of nonruminant protein materials would be limited to single-species facilities, i.e., facilities slaughtering only swine. A renderer could purchase nonruminant protein from more than one single-species facility. The agency believes that this restriction is necessary because of its understanding that it is not likely to be feasible for mixed species slaughterhouses to undertake the additional compliance costs, and possibly additional facility costs, that would be required to assure separation of ruminant and nonruminant materials. The restriction would therefore help assure that enforcement of § 589.2000(e) would be practicable. However, the agency specifically requests comments on this provision.

Third, the firms would be required to establish separate equipment and facilities for the two kinds of materials, or cleanout procedures to prevent cross contamination. Fourth, the firms would need to establish written SOP's specifying the cleanout procedures, if used, and specifying procedures for separating the materials from the time of receipt until the time of shipment. Although § 589.2000(e) applies to several different kinds of firms, the agency's preliminary expectation is that only feed manufacturers and distributors will find it feasible to separate ruminant and nonruminant materials. As an example, a feed manufacturer might obtain ruminant materials from an independent renderer and swine materials from a packer/renderer, and use these materials to manufacture feed both for ruminants and nonruminants. The feed manufacturer would be required to meet the criteria listed previously, including the use of separate equipment and facilities or cleanout procedures, and the establishment of SOP's. The requirements of § 589.2000(e) would be applicable in the transportation process, whether the material is hauled by the feed manufacturer or another party such as an independent hauler. The requirement for separate facilities, procedures or SOP's would not apply to a firm, e.g., a feed mill or hauler, that handles only nonruminant materials, or only ruminant materials. Nor would it apply to a firm that handles both ruminant and nonruminant materials but does not attempt to separate the two kinds of materials.

The paragraph (e) firms would be exempted from the labeling and/or record keeping requirements, and the requirements related to sourcing, facilities and SOP's, if they meet the appropriate criteria for exemption. That is, renderers covered by § 589.2000(e) would be exempt from the labeling and recordkeeping requirements if they used deactivation or detection methods, and from the recordkeeping requirements if they used marking methods. Blenders and feed manufacturers and distributors would be exempt in a similar manner.

Section 589.2000(f) establishes requirements for those who are responsible for feeding ruminant animals. The only requirement contained in this paragraph is that those persons make available to FDA copies of purchase invoices and labeling for all incoming feeds. However, § 589.2000(f) does not apply to the feed manufacturing portion of farms and feedlots that have on-farm feed manufacturing operations. Section 589.2000 (d) and (e) would apply in those instances. Furthermore, persons who feed or intend to feed ruminant protein to ruminant animals would be subject to regulatory action for using or intending to use an unapproved feed additive as established in § 589.2000 (b).

Section 589.2000(g) establishes that violations of § 589.2000 (c) through (f) would cause animal protein products or feed containing animal protein products to be adulterated under sections 402(a)(4) or 402(a)(2)(d) of the act, or misbranded under section 403(a)(1).

Section 589.2000(h) establishes inspection and records retention requirements for persons covered by section 589.2000 (c) through (f). Records that are required under those paragraphs would need to be kept for a minimum of 2 years. The agency believes that this time period is adequate for purposes of verifying compliance with the regulation's procedural requirements. The agency invites comments on the need for a longer retention period related to the BSE incubation period, especially the practicality of using such records for epidemiologic investigation.

Section 589.2000(h) also requires that written procedures required by the regulation be made available for inspection and copying by FDA. The written procedures referred to are those specified in § 589.2000(e)(3). Affected firms would be required to have a copy of the current procedures available at all times.

VII. Specific Protein Sources

A number of comments discussed the exemption of certain tissues, including fluids, from any prohibitory rule. Most commentors favored the exemption of one or more tissues, including milk products; blood products; skeletal muscle and gelatin; and a variety of other tissues including both protein and nonprotein materials. Most of the comments cited published studies as well as positions taken by the European Union, European Commission, WHO and the government of France. The agency's comments on the status of milk, gelatin and blood follow. In addition, we discuss a comment on the use of canine and feline derived protein.

A. Milk Proteins

Data available to the agency suggests that milk proteins do not transmit the TSE agent. Research with oral exposure, intracerebral, and intraperitoneal administration of milk or mammary glands from BSE-infected bovine to normal and BSE-sensitive mice has not demonstrated the development of TSE's (Refs. 42 and 52). An expert group under the auspices of WHO recommended that all countries prohibit the use of ruminant tissues in ruminant feed. The WHO expert group also declared that milk and milk products, including such products from the United Kingdom, are safe for human consumption. In addition, OIE has recommended, because of lack of infectivity, that restriction of import or transit of milk products from healthy animals from BSE countries need not be instituted. Therefore, the proposed rules provide that protein derived from ruminant tissues does not include milk proteins derived from bovine, ovine, caprine, and cervine.

B. Gelatin Proteins

Data available to the agency suggest that gelatin does not transmit the TSE agent. The WHO has concluded that gelatin in the food chain is considered to be safe, as the conventional manufacturing process for gelatin has been demonstrated to significantly inactivate any residual infective activity that may have been present in source tissues (Ref. 2). FDA concurs with this statement and the scientific information on which it is based. Thus, the proposed rule excludes gelatin from protein derived from ruminant tissues.

C. Blood Meal Proteins

Data available to the agency suggests that bovine blood components do not transmit the TSE agent (Refs. 56, 78, and 94). Therefore, the proposed rule does not include blood meal from bovine as a protein derived from ruminant tissues.

D. Canine and Feline Derived Proteins

One comment suggesting that canine- and feline-derived proteins should not be fed to ruminants because of the finding of FSE in domestic cats in the United Kingdom. The agency is also aware of an ethically-based objection by some to the rendering of the carcasses of pet animals. TSE has not been diagnosed in dogs or other canines. FSE has not been diagnosed in the United States. The agency has considered the information provided by the comments and the published scientific literature (Refs. 26 and 27), and has preliminarily determined that there is no measurable risk of the spread of TSE's from canine- or feline-derived proteins to ruminants in the United States. However, the agency is inviting further comment on this issue.

VIII. Environmental Impact

FDA has carefully considered the potential environmental effects of this proposed rule and of five possible alternative actions. In doing so, the agency reviewed ANPRM comments submitted by a number of organizations and individuals. The comments were mostly concerned with the volume of material (e.g., dead animals and slaughter byproducts) that would be affected, and the nonrendering or rendering alternative means by which these materials could be disposed of, or utilized, safely. Comments suggested a number of uses for the processed materials, other than ruminant feed, including use in nonruminant animal feed and fertilizers, and disposal methods such as on-farm burial, landfilling, and incineration.

In the environmental assessment that accompanies this proposed rule, FDA evaluated the environmental consequences of six different options. These included: No action; ruminant and mink-to-ruminant prohibition (the proposed action); partial ruminant and mink-to-ruminant prohibition; mammalian-to-ruminant prohibition; prohibition of feeding tissues from any animal species in which TSE has been detected in the United States; and sheep and goat specified offal prohibition.

The environmental assessment considered each of the alternatives in the context of two scenarios. The first assumes that BSE does not occur in the United States, regardless of the alternative selected. The second scenario assumes that BSE does occur in the United States, again regardless of the alternative selected. In the first scenario, the assessment considered environmental impacts related to on-farm disposal, landfill, incineration, and industry wastes produced. The second scenario considered environmental impacts related to production losses and impacts, wildlife exposure, on-farm disposal, landfill, and incineration.

In the first scenario (no BSE), the ''no action'' alternative does not have environmental consequences because it is the ''status quo'' or baseline alternative. Environmental impacts for the other alternatives ranged from slight to moderate increases in environmental effects. For the proposed option (ruminant-to-ruminant) there would be moderate increases in environmental effects from on-farm disposal and landfill use, and slight increases in the other effects. Increases in waste disposal (on-farm, landfill, etc.) are anticipated to be temporary, however, as the markets are expected to adjust quickly to the more restricted uses of the ruminant materials.

In the second scenario (occurrence of BSE), the greatest negative environmental effect would occur in the case of the ''no action'' alternative. This is because the likely spread of the BSE agent through animal feed before the first BSE case is diagnosed would result in disposal of large numbers of animals by means other than rendering. Similar large impacts would occur with the sheep and goat, and TSE animal, options. Minimum environmental consequences would occur with the proposed option (ruminant-to-ruminant), because the spread of the BSE agent would have been controlled. Minimum to small effects would result from the remaining two options, partial ruminant prohibition and mammalian-to-ruminant prohibition.

The agency has concluded that the proposed rule will not have a significant impact on the human environment, and that an environmental impact statement is not required. FDA's finding of no significant impact (FONSI) and the evidence supporting that finding, contained in an environmental assessment (EA) prepared under 21 CFR 25.31, may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday. FDA invites comments and submission of data concerning the EA and FONSI.

IX. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866, under the Regulatory Flexibility Act (5 U.S.C. 601–612), and under the Unfunded Mandates Reform Act (Pub. L. 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; and distributive impacts and equity). The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. The Unfunded Mandates Reform Act requires that agencies prepare an assessment of anticipated costs and benefits before proposing any rule that may result in an annual expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 (adjusted annually for inflation). FDA

concludes that this proposed rule is consistent with the principles set forth in the Executive Order and in these two statutes.

A study of the impacts on industry of the proposed rule (on file with the Docket Management Branch (Ref. 114)) conducted for FDA by the Eastern Research Group (ERG), a private consulting firm, and the discussion in the remainder of this section, demonstrate that the proposed rule constitutes an economically significant rule as described in the Executive Order. The agency has further determined that the proposed rule will have a significant impact on a substantial number of small entities. The proposal makes no mandates on government entities and is estimated to result in aggregate net annual costs ranging from $21.4 to $48.2 million to the private sector.

A. The Need for Regulation

Although BSE has not been diagnosed in the United States, the need for regulatory action is based on a need to protect U.S. livestock from the risk of contracting BSE. In its guidelines for the preparation of Economic Impact Analyses, the Office of Management and Budget (OMB) directs Federal regulatory agencies to determine whether a market failure exists, and if so, whether that market failure could be resolved by measures other than new Federal regulation. In this instance, private incentive systems for both suppliers and purchasers may fail in markets for cattle, rendering, and ruminant feed. The potential for market failure among the suppliers in these sectors results from the externality that could be created by individual suppliers imposing economic hardships on other suppliers within the industry. The potential for market failure among the purchasers results from the inadequate information that would be available to purchasers of potentially infective products.

Any renderer, feed manufacturer, or cattle producer that permits animal protein derived from ruminants and mink to be placed in ruminant feed increases the risk that other renderers, feed manufacturers, or cattle producers will suffer the severe economic consequences that would follow an outbreak of BSE in the United States. The industry is aware of this risk, as evidenced by the existence of voluntary programs aimed at reducing the transmission of the infectious agent. These include an adult sheep rendering ban recommended by the NRA, a recommended ban on the feeding of rendered ruminant protein to ruminants by the NCBA and others, and scrapie-free certification programs by individual sheep producers. Although the benefits of such programs—the reduction or elimination of the risk of an outbreak of BSE and the increased consumer confidence in the safety of the industries' products—accrue to all members of these industries, compliance with these measures is incomplete, because individual noncomplying members can avoid the costs of risk reduction measures while still enjoying the benefits of compliance by others in the industry.

If purchasers could easily identify the risks of infective agent contamination associated with products from specific suppliers, they could more easily take defensive actions to reduce these risks (e.g., refusing products from cattle known to have consumed specified ruminant proteins). Purchasers are unlikely to obtain the information they need, however, for several reasons. First, the long incubation period for BSE creates a lag between the actual onset and the recognition of the disease and could lead to a suboptimal level of risk prevention by the concerned parties during the incubation period. By the time the first signs of disease are observed, many animals may have been already exposed. Moreover, renderers sell their product to feed manufacturers who frequently combine proteins from many different plant sources and animal species to produce cattle feed. Ruminant producers, therefore, have no sure way of knowing whether a particular batch of feed is free from potentially infective proteins and cannot easily avoid purchasing risky feed. Finally, if renderers or feed manufacturers do not believe that BSE is an important threat they may choose not to take preventive action, regardless of the risk levels perceived by epidemiological experts or consumers.

B. Benefits

The proposed rule would reduce the risk of an outbreak and subsequent proliferation of BSE disease in the United States. It may also forestall the loss of consumer confidence in the U.S. beef market due to concerns about BSE and its implications. Thus, the benefits of this proposal would include the value of reduced risks to human and animal health and to the economic stability of the U.S. livestock and livestock dependent industries compared to the ''no action'' option. In technical terms, these benefits measure the expected value of the future disease-related costs that might be averted by the proposed rule. Specifically, they are calculated as a product of three factors: (1) The probability that, in the absence of this rule, BSE would be introduced and proliferate in the United States, (2) the costs, both direct and indirect, that would be associated with the spread of BSE in the United States, and (3) the extent to which the proposed rule would reduce the likelihood of BSE proliferation.

BSE has not been detected in the United States and the probability that it currently exists is remote. Nevertheless, it is possible that BSE could develop in the future. Once developed, BSE could remain undetected for several years because of its long incubation period and because, at present, it can be diagnosed reliably only by microscopic brain examination after death. During the period between introduction and diagnosis, the disease could spread as it apparently did in the U.K. via intake of infective feed. If regulation was delayed until after discovery, the costs would be substantial. By addressing the central risk factors associated with BSE, FDA believes that the proposed rule would eliminate the vast majority of the BSE-related risks and costs.

BSE was first detected in the U.K. in November 1986, and a ban on ruminant offal in ruminant feed was imposed in the U.K. in July 1988 (Ref. 115). An analysis of cattle born before and after the feed ban went into effect suggests that the feed ban significantly decreased disease transmission (Ref. 116). This analysis found that the incidence of confirmed BSE roughly doubled each year for animals born between July 1985 and July 1988, but declined precipitously in animals born in August 1988 compared to the previous year and continued to fall thereafter. Because BSE has a long incubation period, however, a decrease in the incidence was not evident until several years after the initial feed ban was implemented. The incidence of BSE peaked in 1992 at 36,681 detected cases, or approximately 0.3 percent of the UK's 11.5 million cattle. Despite a sharp decrease in the incidence rate since then, by the end of 1996, more than 165,000 cases of BSE will have been detected, with one-third of all U.K. cattle herds infected (Refs. 115 and 117).

The likelihood that BSE will someday be developed in the United States cannot be estimated with any confidence, although U.S. risk factors are believed to be significantly smaller than existed in the United Kingdom of the early 1980's. As described previously, the various remaining modes include transmission from scrapie-infected sheep or other animals with TSE, e.g., through meat and bone meal; introduction via imported

animals; and spontaneous introduction (which in some TSE's has been hypothesized to occur at a rate of about 1 case per million per year). USDA import controls and the voluntary bans on sheep offal and ruminant tissues in ruminant foods reduce the risk of disease introduction but cannot completely eliminate it.

Although FDA cannot quantitatively estimate the risk of a significant BSE outbreak in the United States, the agency has used the U.K. experience, modified to account for major differences in circumstances, to assess the consequences of the potential spread of the disease within the United States. If BSE were introduced in this country, the pattern of disease spread would presumably be similar to that in the United Kingdom, with most symptomatic disease appearing in older cattle (the average time for BSE symptoms is approximately 5 years after infection (Ref. 115)). The rate of spread of symptomatic disease would probably differ, however, because compared with the pre-BSE U.K. dairy industry, U.S. dairy cows are younger and are exposed to meat and bone meal in feed later in life than was true in the United Kingdom (Ref. 118). United Kingdom dairy animals were historically fed meat and bone meal as calves, whereas U.S. dairy cows ingest meat and bone meal primarily as adults.

1. Methodology

To develop an illustrative estimate of the number of cattle that might be lost to BSE infection if the disease were to occur in the United States in the absence of regulation, FDA extrapolated from the experience in the United Kingdom, but adjusted for the differences in cattle age and potential age of exposure to meat and bone meal. This extrapolation assumes that the detection of BSE in this country would quickly lead to a ruminant-to-ruminant feed prohibition but that, as in the United Kingdom, BSE incidence would nonetheless continue to increase for 6 years due to the disease's long incubation time (hence several years of disease spread before the diagnosis of the first case). To account for the difference in cattle age-related risk factors, FDA assumed that, if BSE occurred in the United States, the affected animals would be predominately dairy cows of age 4 or more, rather than age 3 and up as in the U.K. (due to the differences in age of exposure.) The difference of 1 year is based on the agency's estimate that U.S. cattle are first exposed to meat and bone meal 1 year later than U.K. cattle. Therefore, the onset of the clinical disease is estimated to start 1 year later. Accordingly, only 47 percent of U.S. dairy cows are age 4 and up (about 4.8 million cows), while 90 percent of United Kingdom cows are age 3 and up (about 2.6 million cows). Thus, a lower percentage of U.S. cattle were assumed to be at risk of symptomatic BSE, and the projected rate of death was proportionately lower. Based on the relative size of the U.S. and U.K. dairy cattle populations, these projections suggest that if BSE were introduced in the United States and spread in a similar manner, the disease would destroy 299,000 U.S. cattle over 11 years (4.8 x 2.6 x 162,000 U.K. BSE deaths). (These calculations assume that a feed prohibition would be implemented very soon after the first case is diagnosed, and that the prohibition would immediately begin to affect the underlying rate of new infection. If a feed prohibition were not implemented at that time, the number of cattle deaths would be much higher.)

Other adjustments could be made to this estimate, but their effect on the direction of the results would be uncertain. For example, compared with U.K. practices before 1988, U.S. dairy cattle consume a higher proportion of concentrated feed that contains meat and bone meal. On the other hand, most U.S. concentrate contains a lower percentage of meat and bone meal (and a higher percentage of vegetable-based proteins). If BSE infectivity in feed is highly dose-dependent, these factors could cause FDA's cost estimate to be either too high or too low, if one of the factors is dominant over the other.

The risks and costs associated with BSE when it occurs are primarily of three types. First, there is the possible risk and associated cost of ruminant-to-human transmission of TSE disease. The proposed rule would reduce this risk by eliminating the main routes by which ruminants might acquire transmissible TSE, greatly reducing any risk incurred by the human consumption of ruminant-derived products. Thus, the proposed rule would reduce the risk of future mortality, morbidity, and health care costs due to human TSE. Second, there is the risk of livestock losses. These losses include not only the deaths of BSE-infected animals, but also the loss and disposal costs of other animals that would be destroyed, either to contain the immediate spread of disease or to restore consumer confidence in the safety of beef and dairy products. Third, there are the costs associated with decreased domestic sales and exports of beef and other bovine-derived products until consumer and international confidence could be restored.

2. Reduced Risk to Public Health

As discussed earlier, scientists believe that the nv-CJD cases identified in the U.K. may have been associated with the BSE epidemic. If indeed there were such an association, and if BSE were to occur in this country, there would be a risk of spreading BSE-related human TSE in the United States The proposed rule therefore might avert human deaths in the United States, although the number of deaths cannot be estimated. The proposed rule would also save the health care and other costs associated with treating individuals with the disease.

3. Reduced Risk of Direct Livestock Losses

For estimating the present value of livestock losses if BSE occurred in the United States, FDA assumed that the first case of BSE would not be detected—even in the absence of the proposed rule—for 4 years. Based on an estimated value of $502 per animal (Ref. 119) and disposal costs of $4 per animal, direct losses from the death of 299,000 BSE-infected cattle would reach $151 million over 11 years (starting 4 years from now). At a discount rate of 7 percent, the total present value of these losses is $75 million.

In addition to the animal losses from direct infection, a significant outbreak would probably lead to the eradication of high-risk animals to restore consumer confidence. Switzerland, for example, has proposed slaughtering all cattle born before that country implemented a feed ban, or approximately one-eighth of its national herd (Ref. 120). The United Kingdom has begun a program to destroy and incinerate all animals over age 30 months as they reach the end of their useful life, or about 1 million animals in 1996 and a total of 4.7 million over 6 years. In addition, the United Kingdom has a program to slaughter some unmarketable male dairy calves (126,000 had been slaughtered as of August 1996) and up to 147,000 additional ''high-risk'' animals (Refs. 115 and 121). Even if the U.K. eradication of animals were limited to a one-time total of 1 million cattle (about 8.7 percent of their cattle stock), similar measures in the United States, if they occurred immediately upon detection of the disease, would result in the one-time destruction of $4.58 billion worth of cattle, with a present value of $3.49 billion.

4. Costs of Future Regulation

Moreover, the ability to control a BSE outbreak once it occurred would require putting in place restrictions on the use

of ruminant proteins in ruminant feeds that would be at least as restrictive as the measure under this proposed rule. Presumably, the total costs of implementing a ruminant-to-ruminant feed prohibition at that point would be at least as great as the low estimates for this proposed rule, or $21.4 million per year. The present value of these future regulatory costs would total approximately $240 million. Moreover, this estimate may vastly understate the economic impact because the market value of ruminant-derived proteins could disappear if there were an actual outbreak.

5. Reduced Risk of Losses in Domestic Sales and Exports

If BSE were to emerge in the United States, the news could greatly reduce both domestic sales and exports of bovine products. In the United Kingdom, domestic consumption fell by more than 20 percent between 1988 and 1990 and has not yet fully recovered (Ref. 122), presumably due to continuing concerns about possible links between BSE and CJD. If U.S. consumers acted similarly, U.S. producers of beef products could lose over $9 billion in annual sales (Ref. 123). Alternatively, U.S. consumers might demonstrate considerably less concern, as the U.K. experience may have improved the ability of U.S. risk managers to communicate both the extent of the risk of contracting CJD from the consumption of beef and the responsiveness of the government's safety policies. Nonetheless, it remains probable that the uncertainty surrounding a serious BSE outbreak would lead U.S. consumers to reduce their consumption and spending on beef by a significant amount. Also, at the same time that U.K. domestic sales of beef were declining due to the fear of BSE, the volume of U.K. exported beef fell by nearly 16 percent (Ref. 122). Based on U.S. beef exports in 1994 of approximately $2.2 billion (Ref. 109), a proportional decline of this magnitude would reduce U.S. exports by up to $0.3 billion per year.

While the values of such lost domestic and international sales would reduce the profits of the U.S. beef industry and the enjoyment of some U.S. consumers of beef, they do not provide an accurate measure of societal costs, because competitor industries, such as poultry, pork, and seafood, would gain new profits. Thus, the net costs that would result from such potential shifts in consumer spending cannot be precisely discerned without extensive economic modeling. While FDA examined a partial equilibrium model for projecting the approximate losses of consumer and producer surplus within the market for beef products, the agency could not adequately quantify the likely effects on the markets for substitutes of beef. Consequently, FDA could not estimate the net economic cost of these lost sales. Nevertheless, the magnitude of these potential costs could be substantial and the agency requests public comment on how the appropriate measurement methodologies could be developed and applied.

Finally, even in the absence of evidence of BSE in the United States, consumer concern about BSE could affect beef consumption and expenditures. Thus, one benefit of implementing the proposed rule now is that it might prevent a loss of consumer confidence in the beef market, irrespective of the actual risk of BSE. FDA did not attempt to quantify this potential loss, but believes that it also may be substantial, particularly in light of the recent increased U.S. publicity of BSE and its hypothesized links to CJD.

6. Total Losses Averted

In summary, the losses averted by the proposed rule include the expected value of the costs associated with BSE itself, and the potential value of forestalling a drop in domestic and international demand for U.S. beef due to BSE-related causes. The first component largely reflects the statistical probability that BSE could occur and spread within the United States and the potential $3.7 billion cost of destroying BSE-exposed livestock. The second primarily measures the expected loss to U.S. consumers and producers that would result from reduced sales. While FDA has not quantified these latter costs, plausible scenarios indicate that they could reach billions of dollars. Moreover, these figures have not included the possibility of lost lives and treatment costs associated with treating human TSE.

Finally, the expected benefits of the proposed rule are slightly lower than the sum of the expected value of all the costs associated with BSE, because the rule would not totally eliminate all of the related risk (e.g., due to the possibility of spontaneous introduction of disease and the possible incomplete compliance with the rule). FDA believes, however, that any remaining risk would be extremely small. In addition, because the rate of BSE infection and the associated costs would probably vary geographically (as scrapie does now) (Ref. 98) , the benefits would vary across regions of the country.

7. Comparison of Alternatives

As described elsewhere in this document, FDA is considering five alternatives to the proposed rule, in addition to other options that might be offered in the comments. The first three of these alternatives are: (1) No action (relying on voluntary industry activities), (2) prohibit only materials from U.S. species in which TSE has been diagnosed, and (3) a prohibition on proteins from specified sheep and goat offal in ruminant feed. Compared with the proposed action, prohibiting proteins from all U.S. TSE species provides similar reductions in the risk that BSE might be introduced, with a sheep/goat specified offal protein ban and no action providing progressively less risk reduction. The TSE species alternative, however, would be significantly less effective in limiting the spread of BSE (e.g., after spontaneous introduction) until BSE was diagnosed and cattle were added to the list of TSE species. Likewise, the two other alternatives would be significantly less effective in inhibiting the spread of ruminant-to-ruminant transmission of disease once BSE is introduced. Thus, the expected value of the benefits of each of the three rejected options is substantially lower than the proposed rule, although the amount of difference cannot be estimated precisely.

The agency is also considering two other alternatives: (1) A mammalian-protein-to-ruminant prohibition, and (2) a partial ruminant-to-ruminant prohibition which would exclude all ruminant and mink tissues except certain bovine tissues. Compared with the proposed rule, both alternatives offer similar benefits in substantially inhibiting the initial introduction of BSE. The extent of inhibition of the spread of disease (and associated costs), however, would be different.

The mammalian protein alternative would further reduce the spread of disease compared with the proposed rule, by reducing the risk of cross-contamination within rendering and processing plants. Thus, this alternative would bring the expected value of the BSE-related costs even closer to zero than would the proposed measure. However, the incremental benefit is small if cross- contamination under the proposed measure does not pose a substantial risk.

The partial ruminant-to-ruminant prohibition would be less effective than the proposed measure, because it would be more administratively difficult to enforce. Thus, this alternative would not reduce the expected value of the

BSE-related costs as much as the proposal. Again, however, the exact difference cannot be estimated, but would vary depending on the likely level of compliance under the alternative.

C. Industry Impacts

The ERG study examines the composition, size, and scale of economic activity for the various affected industry sectors and provides estimates of the cost and high and low market impacts (depending on the size of the price change for restricted meat and bone meal of five regulatory options (see Table 1).

TABLE 1.—ESTIMATED COSTS OF ALTERNATIVE REGULATORY PROHIBITIONS [1]

	Mammalian-to-ruminant	Ruminant-to-ruminant (proposal)	Partial ruminant-to-ruminant	Sheep/Mink-to-ruminant	Sheep/Goat-to-ruminant
Annualized Impacts	($ million)				
Low Market Impact Scenario ($25/ton)					
Capital Costs	8.8	1.0	3.2	0.0	0.0
Operating/Disposal Costs	10.1	0.1	14.4	5.1	0.2
Transportation	10.7	7.6	5.3	0.0	0.0
Documentation	1.9	1.5	0.5	0.0	0.0
Substitution Costs	9.7	8.0	3.7	0.0	0.0
Renderer Revenue Losses	76.4	63.2	28.8	4.2	0.1
Nonruminant Gains	(72.6)	(60.0)	(27.4)	0.0	0.0
Totals	45.0	21.4	28.5	9.3	0.3
High Market Impact Scenario ($100/ton)					
Capital Costs	8.8	8.2	4.9	0.0	0.0
Operating/Disposal Costs	10.1	10.1	16.9	5.1	0.2
Transportation	10.7	7.6	5.3	0.0	0.0
Documentation	1.9	1.8	0.7	0.0	0.0
Substitution Costs	9.7	8.0	3.7	0.0	0.0
Renderer Revenue Losses	305.6	252.8	115.4	4.2	0.1
Nonruminant Gains	(290.3)	(240.2)	(109.6)	0.0	0.0
Totals	56.5	48.3	37.3	9.3	0.3

[1] Totals may not match text due to rounding error.

1. The Proposed Rule

The proposed alternative would prohibit the use of ruminant and mink protein in ruminant feeds. Currently, only about 10 percent of the meat and bone meal supply is used in ruminant feed, but over 80 percent of the meat and bone meal contains some ruminant material. ERG forecast that because no mixed-species slaughtering or rendering establishments would find it profitable to separate ruminant from nonruminant offal, most would continue to contain ruminant material. ERG estimated that affected renderers and feedmills would incur total direct compliance costs ranging from $10.2 to $27.6 million per year. Renderers would bear annual costs of about $6.3 million and feed mills would bear annual costs of from $3.8 to $21.3 million. Arrayed by compliance category, transportation costs were estimated at $7.6 million; documentation costs for activities to ensure control of ruminant feed constituents ranged from $1.5 to $1.8 million; and capital costs and operating costs ranged from $1.0 to $8.2 million and $0.1 to $10.1 million, respectively, due primarily to the need for some feedmills to expand their capacity to offer both ruminant and nonruminant feed products under a high market impact scenario.

Because consumer response to the rule is uncertain, ERG could not develop a precise projection of future meat and bone meal prices. ERG estimated, however, that the regulatory prohibition of marketing ruminant meat and bone meal to ruminants would lower the price of this product by from $25 to $100 per ton, decreasing rendering industry revenues by from $63.2 to $252.8 million per year. In contrast, a lower MBM price would increase sales of meat and bone meal to the nonruminant sector and the resulting increased profits for that sector would offset, at an aggregate level, most revenue losses. Although ERG did not quantify this effect, FDA determined that the assumption of a fixed supply of meat and bone meal and a linear demand for nonruminant feed implies that purchasers of mixed-species meat and bone meal for nonruminant uses would save from $60.0 to $240.2 million annually, because of the lower meat and bone meal costs. This estimate assumes a total meat and bone meal supply of 2.5 million tons, changes in price ranging from $25 to $100 per ton, and an increase in nonruminant consumption of meat and bone meal of about 250,000 tons. In addition, manufacturers of ruminant feed would incur higher costs if they could not use ruminant proteins. In an analysis prepared for the feed industry, protein substitutes, such as soybean meal and other minerals necessary to provide the same nutritional level as that provided by the meat and bone meal, were estimated to cost approximately $31.75 per ton more than meat and bone meal (Ref. 125). FDA believes that this estimate is overstated, because it assumes that soybean meal alone sells for $20 per ton more than meat and bone meal. In fact, their respective market prices are currently similar. Nevertheless, FDA used the reported $31.75 per ton differential to estimate that the higher price of alternative proteins would increase ruminant feed costs by about $8.0 million per year.

As a result, FDA estimates that the aggregated annualized costs of this proposal, comprised of both the direct compliance costs and the various indirect gains and losses, would total

from $21.4 to $48.2 million. Although the greatest initial burden would fall on the rendering and feed manufacturing sectors, ERG noted that the final distribution of these impacts would shift; renderers would pass back the economic impacts to slaughterers, who, in turn, would pass them back to cattle producers. FDA judged, however, that of the small renderers dependent upon farmers' and ranchers' dead stock for their raw materials, 20 to 25 would be likely to close. ERG also forecast that these impacts would cause a decline in prices for slaughter-weight cattle of $1 to $5 per head. In the long run, ERG foresaw a modest reduction in the size of the U.S. cattle herd.

In response to its ANPRM, FDA received comments on the possible impacts of the proposal from both individuals and industry. The submission from the American Feed Industry Association (AFIA) contained an analysis of the animal feed market that was based on the assumption that the proposal would taint the safety of all meat and bone meal (both ruminant and nonruminant), to the extent that even nonruminant animal producers would refuse to purchase the product. This loss of wholesale value was estimated at $523 million. Further, the AFIA comment estimated the cost for disposing of this meat and bone meal at $349 million and for substituting to higher priced feeds at $74 million annually.

FDA questions the conclusions of the AFIA report, largely because the proposed rule does not prohibit the use of ruminant proteins in nonruminant feeds and there is no evidence that this market would disappear. As noted earlier, nonruminant feed use currently constitutes about 90 percent of the meat and bone meal market. While some nonruminant producers may be wary of ruminant MBM after the proposal becomes final, the broad media coverage of BSE in the United Kingdom and the voluntary prohibition of ruminant MBM in ruminant feeds have already provided nonruminant producers with substantial information on the relevant risks. The implications of the ERG study are that most of the major nonruminant sectors that use ruminant meat and bone meal in their feeds would continue this practice, particularly at sharply lower MBM prices. Because ERG believed that all stocks of meat and bone meal would find a commercial outlet within the nonruminant feed sector, they projected no additional disposal costs and far smaller revenue losses than AFIA.

2. Partial Ruminant-to-Ruminant Prohibition

ERG also estimated the economic impact of a partial ruminant-to-ruminant prohibition, which would prohibit only the use of proteins from designated ruminant tissues in ruminant feeds. ERG projected that cattle packer/renderers and approximately one-half of the large cattle packers would choose to separate the designated and nondesignated tissues. As shown in Table 1, this change in processing would lead to increased costs from capital investments, increases in operating and transportation expenses, training, and documentation activities. Further, ERG projected, under the high market impact scenario, that some feedmills would expand their facilities to offer both restricted and nonrestricted meat and bone meal. They estimated the annualized direct compliance costs for this option at from $23.5 to $27.9 million. In addition, ERG projected that this option would cause price declines of from $25 to $100 per ton for the meat and bone meal derived from designated tissues, leading to decreases in renderer revenues of from $28.8 to $115.4 million per year. As discussed previously, FDA again assumed a fixed supply of meat and bone meal and a linear demand for nonruminant feed to calculate that purchasers of mixed-species meat and bone meal for nonruminant uses would save from $27.4 million to $109.6 million annually because of the lower meat and bone meal costs. Adding additional protein substitution costs of $3.7 million and other indirect costs raises the estimated net aggregate costs for this alternative to $28.6 to $37.4 million.

3. Mammalian-to-Ruminant Prohibition

The third option assessed was the prohibition of mammalian protein in ruminant feeds. ERG projected that slaughtering and rendering establishments would have no reason to separate offal because very few of these establishments process both mammals and nonmammals. They estimated annualized direct compliance costs for this option at $31.6 million. ERG forecast that, regardless of the size of the price decline for restricted meat and bone meal, some feedmills would expand their capacity to offer both restricted and nonrestricted meat and bone meal, resulting in increased capital and plant operating costs. The majority of the remaining regulatory costs are composed of documentation costs. Assuming that a regulatory prohibition on marketing restricted meat and bone meal to ruminants would cause the price of the restricted meat and bone meal to fall by from $25 to $100 per ton, ERG projected that this option would reduce renderer revenues by from $76.4 to $305.6 million per year. Alternatively, under the same assumptions as applied above, FDA found that purchasers of mixed-species meat and bone meal for nonruminant uses would save from $72.6 million to $290.3 million annually, because of the lower meat and bone meal costs. Adding additional protein substitution costs of $9.7 million and other indirect costs raises the estimated net aggregate costs for this third option to from $45.1 to $56.6 million.

4. Other Regulatory Alternatives

FDA also considered two less restrictive options for controlling the spread of an outbreak of BSE in the United States: A prohibition of all sheep, goat, mink, deer, and elk proteins in ruminant feed; and a prohibition of sheep and goat proteins in ruminant feed. The first of these alternatives would require that ruminants not be fed proteins from any species in which a TSE was diagnosed in the United States, which includes sheep, goats, mink, deer, and elk. ERG anticipated minimal regulatory impacts for sheep, lamb, and goat producers because most renderers already require that sheep, lamb, and goat offal be excluded from mixed species meat and bone meal. ERG estimated that this alternative could restrict the use of up to 34,150 tons of offal annually from the various species, or about 0.3 percent of all mammalian offal rendered. Using an estimated cost of $150/ton for landfill disposal, ERG calculated that the disposal costs for this alternative could equal $5.1 million. Furthermore, ERG estimated that the meat and bone meal and tallow manufactured from offal generates revenues of about $500/ton of processed material. Under this option, meat and bone meal production would fall by 8,450 tons per year, reducing industry revenues by an estimated $4.2 million annually.

The final alternative would restrict only sheep and goat protein from use in ruminant feed. This alternative is similar to the agency's 1994 proposal, which pertained only to adult sheep and goats. Most sheep and goats are currently excluded by renderers from being rendered into mixed species meat and bone meal. ERG estimated that this alternative would restrict the use of up to 1,200 tons of offal, or about 0.01 percent of all mammalian offal rendered. At $150/ton for landfill disposal, the disposal costs would equal $0.2 million. ERG calculated that

production of meat and bone meal under this option would be restricted by only 300 tons per year, leading to revenue losses of about $0.1 million.

ERG noted that the disposal costs presented for the latter two alternatives are high-end estimates because of the likelihood of onsite disposal for deer and elk taken by hunters. Further, these alternatives were not expected to have a measurable effect on the price of meat and bone meal because they would affect only 0.3 percent and 0.01 percent of the meat and bone meal markets, respectively. In contrast to the first three options, these rules would not change the demand for meat and bone meal, but would restrict the supply of meat and bone meal. Any postregulation increase in price, therefore, would increase revenues of renderers and costs of purchasers of meat and bone meal by an almost equal amount. ERG reported that this decrease in supply would have a negligible effect on meat and bone meal prices.

D. Small Business Impacts

The Regulatory Flexibility Act requires agencies to prepare a regulatory flexibility analysis if a rule would have a significant impact on a substantial number of small entities. The discussion in this section, as well as in other sections of this document, and the ERG report, constitute the agency's compliance with this requirement.

The Regulatory Flexibility Act asks for a succinct statement of the purpose and objectives of the rule. As explained previously in this document, FDA is proposing this measure to address the risk to U.S. livestock associated with feeding ruminant proteins to ruminants. Existing epidemiological evidence suggests a link between an outbreak of BSE in the United Kingdom and the practice of feeding products to cattle that included ruminant proteins. This rule would prohibit that practice. Thus, the need for regulatory action is based on the need to prevent the spread of BSE and thereby to protect the health of animals and to minimize any risk that might be posed to humans from BSE.

The Regulatory Flexibility Act also requires a description of the affected small entities. The ERG study includes counts of entities in each class of industry that are involved in ruminant production and meat preparation. The vast majority of all of these firms are considered small businesses according to size standards set by the Small Business Administration. There are 282 rendering plants, of which 204 have fewer than 500 employees, including all of the 152 independent renderers. ERG also estimated that 30,000 feedmills, all with fewer than 500 employees, could be affected by this rule. An estimated 1.4 million enterprises are engaged in ruminant production. These include businesses engaged in the production of beef and dairy cattle, including farmers and ranchers, stocker operators, and cattle feeders, and other ruminant producers. The slaughtering industry contains more than 4,000 establishments. Of this total, however, only 130 are packer/renderers that could have compliance requirements and about 52 of these establishments have fewer than 500 employees. ERG estimated that almost 300,000 small establishments are engaged in meat processing. These businesses would have no direct compliance activities, but could be affected indirectly by altered renderer practices. Also, about 150,000 small producers of nonruminant animals could gain from lower feed costs.

The RFA also requires a description of the recordkeeping requirements of the proposed rule. The ERG report presents detailed estimates of these costs. ERG found that the rule would require certain feed manufacturers to develop new written operating procedures. In addition, affected firms would have to retain invoices but FDA believes this activity is already generally accepted business practice.

Finally, the Regulatory Flexibility Act asks for an evaluation of any regulatory overlaps and regulatory alternatives that would minimize costs to small entities. FDA is unaware of any significant regulatory conflicts with other Federal rules. FDA examined five regulatory alternatives in addition to no action: (1) The ruminant-to-ruminant prohibition; (2) the partial ruminant-to-ruminant prohibition; (3) the mammalian-to-ruminant prohibition; (4) the prohibition of all sheep, goat, mink, deer, and elk proteins in ruminant feed; and (5) the prohibition of specified sheep and goat proteins in ruminant feed. The ERG report provides a detailed comparison of the respective impacts of these alternatives and found that the estimated direct compliance costs are lower under the proposed rule ($10.2 to $27.6 million) than under two of the alternative rules ($23.5 to $27.9 million for the partial ruminant-to-ruminant option, $31.6 million for the mammalian-to-ruminant option). The other alternatives would not be nearly as effective at reducing the risk of an outbreak and spread of BSE, but are considerably less costly. As many of the above projections are uncertain, FDA particularly invites additional data or comment on the effects of the proposed and alternative rules on any group of small businesses.

E. Unfunded Mandates Analysis

Based on the ERG study, FDA estimated that aggregate expenditures by the private sector that result from the proposed rule, issued under 21 CFR 589.2000, will range from $10.2 to $27.6 million per year. As described in section IX.B. of this document, the benefits of this measure accrue both to the general public (through decreased risks to health) and to the livestock and associated industries. The costs of the measure are borne by the private sector, primarily the rendering and animal feed industries. Because FDA anticipates no significant additional costs to State, local, or tribal governments, this regulatory action does not require an assessment under the Unfunded Mandates Reform Act.

X. The Paperwork Reduction Act of 1995

This proposed rule contains recordkeeping requirements that are subject to public comment and review by OMB under the Paperwork Reduction Act of 1995 (Pub. L. 104–13). Therefore, in accordance with 5 CFR part 1320, a description of reporting requirements is given in Table 2 of this document, with an estimate of the annual collection of information burden. Included in the estimate is the time for reviewing instructions, gathering and maintaining the data needed, and completing and reviewing the collection of information.

With respect to the following collection of information, FDA is soliciting comments on: (1) Whether the proposed collection of information is necessary for proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on those who are to respond, including through the use of automated collection techniques or other forms of information technology, when appropriate.

Title: Substances Prohibited from Use in Animal Food or Feed; Animal Proteins Prohibited in Ruminant Feed.

Description: The proposed rule (§ 589.2000) provides that protein derived from ruminant and mink tissues is not GRAS for use in ruminant feed and is a food additive subject to section 409 of the act. Proteins derived from

animal tissues contained in such feed ingredients in distribution cannot be readily determined by recipients engaged in the manufacture, processing and distribution, and use of animal feeds and feed ingredients. To achieve the public and animal health objectives of this proposed rule, the agency believes that manufacturers, processors, distributors, and users must be responsible for ensuring and appropriately maintaining the identity of the specific nature of the components of animal protein products and animal feeds containing these products.

Thus, under the agency's authority in section 701(a) (21 U.S.C. 371(a)) of the act to issue regulations for the efficient enforcement of the act, this proposed rule places three general requirements on persons that manufacture, blend, process and distribute products that contain or may contain protein derived from ruminant and mink tissues, and feeds made from such products. The first requirement is for cautionary labeling of these products with direct language developed by FDA. The second requirement is for these establishments to provide FDA with access to their purchase and sales invoices for compliance purposes. FDA believes that maintenance of such records is a usual and customary part of normal business activities for such firms. These two requirements are not within the scope of the Paperwork Reduction Act. The third requirement is recordkeeping which requires that the firms develop standard operating procedures if they intend to keep ruminant and mink material separate from nonruminant material. The agency is aware that the certification procedures provided in § 589.2000(d) of the regulation could be interpreted as imposing a paperwork burden on certain industry segments. However, the agency notes that the certification procedures apply only where new technology (e.g., a deactivation method) is developed. The agency was unable to estimate when such technology might be developed, what its characteristics and costs would be, and other essential information needed to make realistic estimates of any paperwork burden. Therefore, such costs are not included in this proposed rule. However, the agency specifically requests comments and information related to the factors that would determine the extent of any paperwork burden.

The recordkeeping burden in Table 2 has been estimated using the typical average size establishment that is expected to handle animal protein from both ruminant and nonruminant sources, or feeds containing these products, and intend to keep them separate. FDA's preliminary estimate is that only a fraction of feed manufacturers and distributors will separate their products. Independent renderers were excluded from the burden estimates based on information provided for the economic estimate. Packer/renderers were excluded because they are single species processors.

Under these recordkeeping requirements, for which records must be made available for FDA inspection, an estimated 2,000 feed mills would handle both restricted and nonrestricted products and would develop standard operating procedures for keeping ruminant and mink material separate from nonruminant material from the time of receipt to time of shipment. The estimate in the burden chart is based on the time required to develop and establish the written procedures and is a one time requirement. The 2,000 firms will also incur annual operating cost estimated at $10 million, because of the flushing, sequencing and other procedures that will be required. It is estimated that 1,000 of the firms may incur capital cost for the construction of separate facilities. These costs have been annualized for 10 years, at $7.119 million per year. The remaining firms are expected to be able to meet the regulation's requirements without incurring capital cost.

The agency has submitted copies of the proposed rule to OMB for its review of these requirements. Interested persons are requested to send comments regarding this collection of information by February 18, 1997, but not later than March 4, 1997 to the Office of Information and Regulatory Affairs, OMB (address above), Attn: Desk Officer for FDA.

Description of Respondents: Distributors, feed manufacturers, blenders and renderers.

TABLE 2.—ESTIMATED ANNUAL RECORDKEEPING BURDEN [1]

21 CFR section	No. of record keepers/ firms	Frequency	Total annual records	Hours per record	Total hours	Capital cost (annualized)	Operating cost (yearly)
589.2000 (e)(1)(iv)	2,000	1	2,000	14	28,000	$7,119,000	$10,000,000

[1] Costs are only incurred under the high-impact scenario.

XI. Federalism

FDA has analyzed this proposal in accordance with the principles and criteria set forth in Executive Order 12612 and has determined that this proposal does not warrant the preparation of a Federalism Assessment.

XII. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Transcript, FDA and USDA Symposium, ''Tissue Distribution, Inactivation and Transmission of Transmissible Spongiform Encephalopathies,'' Riverdale, MD, 1996.

2. WHO, ''Report of a WHO Consultation on Public Issues Related to Human and Animal Transmissible Spongiform Encephalopathies,'' With the participation of FAO and OIE, Geneva, Switzerland, WHO/EMC/DIS/96.147, 2–3 April 1996.

3. Centers for Disease Control and Prevention, Memorandum, July 25, 1996.

4. USDA, APHIS, ''Bovine Spongiform Encephalopathy: Implications for the United States, a Follow-up,'' 1996.

5. Personal Communications, Will Hueston, 1996.

6. Walker, K. D., et al., ''Comparison of bovine spongiform encephalopathy risk factors in the United States and Great Britain,'' Journal of the American Veterinary Medicine, 199(11):1554, 1991.

7. Foster, J. D., et al., ''Studies on Maternal Transmission of Scrapie in Sheep,'' *Veterinary Record*, 130:341–343, 1992.

8. Hadlow, W. J., R. C. Kennedy, and R. E. Race, ''Natural Infection of Suffolk Sheep With Scrapie Virus,'' *Journal of Infectious Diseases*, 146:657, 1982.

9. Kimberling, C. V., ''Jensen and Swift's Diseases of Sheep,'' Lea and Febiger, pp. 336–340, 1988.

10. Detweiler, L. A., ''Scrapie, Revue Scientifique et Technique,'' Office Internationale Epizootics, 11(2):491–537, 1992.

11. USDA, APHIS, Veterinary Services, ''Fact Sheet: Scrapie,'' June 1993.

12. Davis, A., USDA–APHIS–U.S., personal communication, April 1996.

13. Bradley, R., ''Editorial: Bovine Spongiform Encephalopathy: The Need for Knowledge, Balance, Patience, and Action,'' *Journal of Pathology*, 160:283–285, 1990.

14. Hueston, W., ''Clinical Signs of BSE, Animal Health Insight,'' Summer:4, 1991.

15. Wilesmith, J. W., G. A. H. Wells, M. P. Cranwell, and J. B. M. Ryan, ''Bovine Spongiform Encephalopathy: Epidemiological Studies,'' *Veterinary Record*, 123:638–644, 1988.

16. Wells, G. A. H., et al., ''Bovine Spongiform Encephalopathy: Diagnostic Significance of Vacuolar Changes in Selected Nuclei of the Medulla Oblongata,'' *Veterinary Record*, 125:521–524, 1989.

17. Davis, A. J., A. L. Jenny, and L. D. Miller, ''Diagnostic Characteristics of Bovine Spongiform Encephalopathy,'' *Journal of Veterinary Diagnostic Investigations*, 3:266–271, 1991.

18. Dx monitor, USDA-APHIS-US, Spring, 1996.

19. Chen, S. S., et al., ''Bovine Spongiform Encephalopathy Identified in a Cow Imported to Canada from the U.K.—A Case Report,'' *Canadian Veterinary Journal*, January 1996.

20. Marsh, R. F., and R. A. Bessen, ''Epidemiologic and Experimental Studies on Transmissible Mink Encephalopathy,'' in Transmissible Spongiform Encephalopathy-Impact on Animal and Human Health, 80:105–112, 1993.

21. Williams, E. S., and S. Young, ''Neuropathology of Chronic Wasting Disease of Mule Deer and Elk,'' *Veterinary Pathology*, 30:36–45, 1993.

22. Williams, E. S., and S. Young, ''Chronic Wasting Disease of Captive Mule Deer: A Spongiform Encephalopathy,'' *Journal of Wildlife Diseases*, 16–1:89–98, 1980.

23. Fleetwood, A. J., and C. W. Furley, ''Spongiform Encephalopathy in an Eland,'' *Veterinary Record*, April 21, 1990.

24. Jeffrey, M., and G. A. H. Wells, ''Spongiform Encephalopathy in a Nyala,'' *Veterinary Pathology*, 25:398–399, 1988.

25. Kirkwood, J. K., et al., ''Spongiform Encephalopathy in an Arabian Oryx and a Greater Kudu,'' *Veterinary Record*, 127, 17:418–420, 1990.

26. Wyatt, J. M., et al., ''Naturally Occurring Scrapie-like Spongiform Encephalopathy in Five Domestic Cats,'' *Veterinary Record*, 129:233–236, 1991.

27. Laggett, M. M., J. Dukes, and H. M. Pirie, ''A Spongiform Encephalopathy in a Cat,'' *Veterinary Record*, 1990.

28. Dealler, S. F., and R. W. Lacey, ''Transmissible Spongiform Encephalopathies,'' in Encyclopedia of Microbiology, edited by Joshua Lederberg, vol. 4, Academic Press, Inc., San Diego, CA, 1992.

29. Centers for Diseases Control, ''Report of Meeting on Creutzfeldt-Jakob Disease and Bovine Spongiform Encephalopathy,'' Atlanta, GA, April 8, 1996.

30. Will, R. G., J. W. Ironside, and M. Zeibeler, et al., A new variant of ''Creutzfeldt-Jakob Disease in the United Kingdom,'' *Lancet*, 347:921–925, 1996.

31. Goldfarb, L. G., R. B. Petersen, M. Tabaton, P. Brown, A. C. LeBlanc, P. Montagna, P. Cortelli, J. Julien, C. Vital, and W. W. Pendelbury, et al., ''Fatal Familial Insomnia and Familial Creutzfeldt-Jakob Disease: Disease Phenotype Determined by a DNA Polymorphism,'' *Science*, 258(5083):806–808, 1992.

32. Seilhean, D., C. Duyckaerts, and J. J. Hauw, ''Insomnie Fatale Familiale et Maladies a Prions,'' *Revue Neurologique*, 151(4):225–230, 1995.

33. Collinge, J., M. S. Palmer, K. C. Sidle, I. Gowland, R. Medori, J. Ironside, and P. Lantos, ''Transmission of Fatal Familial Insomnia to Laboratory Animals (letter),'' Lancet, 346(8974):569–570, 1995.

34. Schreuder, B. E. C., ''BSE Agent Hypothesis,'' *Livestock Production Science*, 38:23–33, 1994.

35. Brooks, B. R., et al., ''Spongiform Polioencephalomyelopathy Caused by a Murine Retrovirus,'' *Laboratory Investigation*, 43;480, 1980.

36. Bastian, F. O., et al., ''Neuropathology of Spiroplasma Infection in the Rat Brain,'' *American Journal of Pathology*, 114:496–514, 1984.

37. Gray, A., et al., ''Spiroplasma and Creutzfeldt Disease,'' *Lancet*, 2:152, 1980.

38. Purdey, M., ''Are Organophosphate Pesticides Involved in the Causation of Bovine Spongiform Encephalopathy? Hypothesis Based Upon a Literature Review and Limited Trials on BSE Cattle,'' *Journal of Nutritional Medicine*, 4:43–82, 1994.

39. Edlin, G., ''The Senile Dementia: a New Model,'' *Medical Hypotheses*, 27:29–31, 1988.

40. DeArmond, S. J. and Prusiner, S. B., ''Prion Diseases,'' *Psychopharmacology: The Fourth Generation of Progress*, Chapter 131, p. 1521, 1995.

41. Lansbury, P.T. and Caughey, B., ''The Chemistry of Scrapie Infection: Implications of the 'ice 9' Metaphor,'' Chemistry & Biology, 2:1, 1995.

42. Muramoto, M., et al., ''Accumulation of Abnormal Prion a Protein in Mice Infected With Creutzfeldt-Jacob Disease Via Intraperitoneal Route: A Sequential Study,'' *American Journal of Pathology*, 143:1470–1479, 1993.

43. Scott, J. R., and H. Frasier, ''Transport and Targetting of Scrapie Infectivity and Pathology in the Optic Nerve Projections Following Intraocular Infection,'' *Progress in Clinical Biological Research*, 317:645–652, 1989.

44. Clarke, M. C., et al., ''Presence of the Transmissible Agent of Scrapie in the Serum of Affected Mice and Rats,'' *Veterinary Record*, 80(16):504, 1967.

45. Field, E. J., et al., ''Scrapie Agent in Blood,'' *Veterinary Record*, 83:109, 1968.

46. Diringer, H., ''Sustained Viremia in Experimental Hamster Scrapie,'' *Archives of Virology*, 82:105–109, 1984.

47. Casaccia, P., et al., ''Levels of Infectivity in the Blood Through the Incubation Period of Hamsters Peripherally Injected with Scrapie,'' *Archives of Virology*, 108:145–149, 1989.

48. Manuelidis, E. E., et al., ''Transmission to Animals of Creutzfeldt-Jacob Disease from Human Blood,'' *Lancet*, 2:896–897, 1985.

49. Manuelidis, E. E., et al., ''Viremia in Experimental Creutzfeldt-Jacob Disease,'' *Science*, 200:1069–1070, 1978.

50. Gibbs, C. J., et al., ''Viral Characteristics of the Scrapie Agent in Mice, National Institute of Neurological Diseases and Blindness Monograph No. 2,'' Slow, Latent, and Temperate Virus Infections, 195–202, 1965.

51. Middleton, D. J., and Barlow, ''Failure to Transmit Bovine Spongiform Encephalopathy to Mice by Feeding Them with Extraneural Tissues of Affected Cattle,'' *Veterinary Record*, 132:545–547, 1993.

52. Taylor, D. M., C. E. Ferguson, C. J. Bostock, and M. Dawson, ''Absence of Disease in Mice Receiving Milk from Cows with Bovine Spongiform Encephalopathy,'' *Veterinary Record*, 136:592, 1995.

53. Ministry of Agriculture Fisheries and Food (MAFF), ''Reports of a Decline in the Incidence of BSE,'' *Veterinary Record*, p. 26, 1995.

54. Hadlow, W. J., et. al., ''Virologic and Neurohistopathologic Findings in Dairy Goats Affected with Natural Scrapie,'' *Veterinary Pathology*, 17:187–199, 1980.

55. Hotchin, J., et al., ''Disappearance of Scrapie Virus from Tissue of the Mouse,'' *Intervirology*, 19:205–212, 1983.

56. Ministry of Agriculture, Fisheries and Food, ''Bovine Spongiform Encephalopathy in Great Britain: A Progress Report,'' November 1995.

57. Diedrich, J. F., et al., ''Increased Expression of Heat Shock Protein, Transferrin, and B2–Microglobulin in Astrocytes During Scrapie,'' *Microbial Pathogenisis*, 15:1–6, 1993.

58. Forloni, G., et al., ''Neurotoxicity of a Prion Protein Fragment,'' *Nature*, 362:543–546, 1993.

59. Fairbairn, D. W., et al., ''Spongiform Encephalopathies and Prions: An Overview of Pathology and Disease Mechanisms,'' FEMS Microbiology Letters, 123:233–240, 1994.

60. Brown, D. R., et al., ''Role of Microglia and Host Prion Protein in Neurotoxicity of a Prion Protein Fragment,'' *Nature*, 380:345–347, 1996.

61. Hsiao, K., ''Mutation of the Prion Protein in Libyan Jews With Creutzfeldt-Jakob Disease,'' *New England Journal of Medicine*, 324:1091–1097, 1991.

62. Onodera, T., et al., ''Isolation of Scrapie Agent from the Placenta of Sheep with Natural Scrapie in Japan,'' *Microbiology and Immunology*, 37:311–316, 1993.

63. Foster, J. D., et al., ''Transmission of Bovine Spongiform Encephalopathy to sheep and goats,'' Veterinary Record, 133(14):339, 1993.

64. Goldman, W., et al., ''PrP genotype and agent effects in scrapie: change in allelic interaction with different isolates of agent in sheep, a natural host of scrapie,'' Journal of General Virology, 75(5):989, 1994.

65. Foster, J. D., et al., ''Detection of BSE infectivity in brain and spleen of experimentally infected sheep,'' Veterinary Record, 138:546, 1996.

66. Gordon, W. S., ''Transmission of Scrapie and Evidence of Spread of Infection in Sheep at Pasture,'' Report at Scrapie Seminar, Washington, DC, January 27–30, 1964; ARS 91—53:8–18, 1966.

67. Wisniewski, H., et al., ''Mites as Vectors for Scrapie,'' *Lancet*, 347:1114, 1996.

68. Goldfarb, L. G., R. B. Petersen, M. Tabaton, P. Brown, A. C. LeBlanc, P. Montagna, P. Cortelli, J. Julien, C. Vital, and W. W. Pendelbury, et al., ''Fatal Familial Insomnia and Familial Creutzfeldt-Jakob Disease: Disease Phenotype Determined by a DNA polymorphism,'' *Science,* 258(5083): 806–808, 1992.

69. Ghetti, B., S. R. Dlouhy, G. Giaccone, O. Bugiani, B. Frangione, M. R. Farlow, and F. Tagliavini, Gerstmann-Straussler-Scheinker Disease and the Indiana Kindred, Brain Pathology, 5:61–75, 1995.

70. Kitamoto, T., M. Ohta, K. Doh-ura, S. Hitoshi, Y. Terao, and J. Tateishi, ''Novel Missense Variants of Prion Protein in Creutzfeldt-Jakob Disease or Gerstmann-Straussler Syndrome,'' *Biochemical and Biophysical Research Communication,* 191: 709–714, 1993.

71. Oda, T., T. Kitamoto, J. Tateishi, T. Mitsuhashi, K. Iwabuchi, C. Haga, E. Oguni, Y. Kato, I. Tominaga, and K. Yanai, et al., ''Prion Disease with 144 Base Pair Insertion in a Japanese Family Line,'' *Acta Neuropathologica,* 90:80–86, 1995.

72. Tateishi, J., and T. Kitamoto, ''Inherited Prion Diseases and Transmission to Rodents,'' *Brain Pathology,* 5:53–59, 1995.

73. Ikeda, T., M. Horiuchi, N. Ishiguro, Y. Muramatsu, G. D. Kai-Uwe, and M. Shinagaw, ''Amino Acid Polymorphisms of PrP with Reference to Onset of Scrapie in Suffolk and Corriedale Sheep in Japan,'' *Journal of Genetic Virology,* 76:2577–2581, 1995.

74. Belt, P. B., I. H. Muileman, B. E. Schreuder, J. Bos-de-Ruijter, A. L. Gielkens, and M. A. Smits, ''Identification of Five Allelic Variants of the Sheep PrP Gene and Their Association with Natural Scrapie,'' *Journal of Genetic Virology,* 76:509–517, 1995.

75. Westaway, D., V. Zuliani, C. M. Cooper, M. Da-Costa, S. Neuman, A. L. Jenny, L. Detwiler, and S. B. Prusiner, ''Homozygosity for Prion Protein Alleles Encoding Glutamine-171 Renders Sheep Susceptible to Natural Scrapie,'' *Genes and Development,* 8:959–969, 1994.

76. Clouscard, C., P. Beaudry, J. M. Elsen, D. Milan, M. Dussaucy, C. Bounneau, F. Schelcher, J. Chatelain, J. M. Launay, and J. L. Laplanche, ''Different Allelic Effects of the Codons 136 and 171 of the Prion Protein Gene in Sheep with Natural Scrapie,'' *Journal of Genetic Virology,* 76:2097–2101, 1995.

77. Hunter, N., W. Goldmann, G. Smith and J. Hope, ''Frequencies of PrP Gene Variants in Healthy Cattle and Cattle with BSE in Scotland,'' *Veterinary Record,* 135:400–403, 1994.

78. Kimberlin, R. H., ''Bovine Spongiform Encephalopathy,'' *Scientific and Technical Review,* 11:347–390, 1992.

79. Schmerr, et al., *Journal of Chromatography,* in press.

80. Beekes, M., et al., ''Western Blot Mapping of Disease-Specific Amyloid in Various Animal Species and Humans with Transmissible Spongiform Encephalopathies Using a High-yield Purification Method,'' *Journal of General Virology,* 76:2567–2576, 1995.

81. Banissi-Sabourdy, C., et al., ''Electroanalytical Characterization of Alzheimer's Disease and Ovine Spongiform Encephalopathy by Repeated Cyclic Volummetry at a Capillary Graphite Paste Electrode,'' *Bioelectrochemistry and Bioenergetics,* 28:127–147, 1996.

82. Gibbs, C. J., et al., personal communications, 1996.

83. Schreuder, B. E. C., et al, ''Preclinical Test for Prion Diseases,'' *Nature,* 381:563, 1996.

84. Hsich, g., et al, ''The 14–3–3 Brain Protein in Cerebrospinal Fluid as a Marker for Transmissible Spongiform Encephalopathies,'' *NEJM,* 335:924, 1996.

85. Taylor, D. M., S. L. Woodgate, and M. J. Atkinson, ''Inactivation of the Bovine Spongiform Encephalopathy Agent by Rendering Procedures,'' *Veterinary Record,* 9(137):605–610, 1995.

86. Taylor, D. M. and R. Bradley, personal communication, 1996.

87. Collee, J. G., ''Food Borne Illness-Bovine Spongiform Encephalopathy,'' *Lancet,* 336:1300–1303, 1990.

88. Fraser, H., et al., ''Transmission of Bovine Spongiform Encephalopathy and Scrapie to Mice,'' *Journal of General Virology,* 73:1891–1897, 1992.

89. Robinson, M. M., ''Bovine Spongiform Encephalopathy,'' Foreign Animal Disease, pp. 134–138, 1992.

90. Spongiform Encephalopathy Advisory Committee, United Kingdom, statement, March 20, 1996.

91. WHO, ''Scientific Consultation on Human and Animal Spongiform Encephalopathies,'' Geneva, Switzerland, 16-17 May 1996, Press Release WHO/38.

92. Lasmezas, C. I., et al, ''BSE Transmission to Macaques,'' *Nature,* 381:743, 1996.

93. Collinge, J., et al., ''Molecular analysis of prion strain variation and the aetiology of 'new variant' CJD,'' *Nature,* 383:685, 1996.

94. World Health Organization, ''Report of a WHO Consultation on Public Health Issues Related to Human and Animal Transmissible Spongiform Encephalopathies,'' WHO/CDS/PH/95.145, 1995.

95. Hueston, Will, USDA, personal communication, 1996.

96. Centers for Disease Control and Prevention, ''Surveillance for Creutzfeld-Jakob Disease—United States,'' Morbidity and Mortality Weekly Report, 45(31):665, 1996.

97. USDA, ''Animal and Plant Health Inspection Service, Emergency Programs Activities, Bovine Spongiform Encephalopathy (BSE) Surveillance Program,'' in Foreign Animal Disease Report, No. 20–3/4, pp. 1–2, 1992, and poster display at U.S. Animal Health Association annual meeting, October 30, 1993.

98. USDA, APHIS, ''Qualitative Analysis of BSE Risk Factors in the United States,'' 1991.

99. USDA, APHIS, ''Bovine Spongiform Encephalopathy: Implications for the United States,'' 1993.

100. Holman, R. C., A. S. Khan, J. Kent, T. W. Strine, and L. B. Schonberger, ''Epidemiology of Creutzfeldt-Jakob Diseases in the United States,'' 1979–1990: Analysis of National Mortality Data, *Neuroepidemiology,* 14:174–181, 1995.

101. CDC, ''World Health Organization Consultation on Public Health Issues Related to Bovine Spongiform Encephalopathy and the Emergence of a New Variant of Creutzfeldt-Jakob Disease,'' *Morbidity and Mortality Weekly Report,* 45/(14):295–303, 1996.

102. Office Internationale Epizootics, International Animal Health Code, Chapter 3.2.13 on BSE, pp. 231–235, July 1993.

103. European Community decisions, 96/362/EC.

104. Bisplinghoff, F. D., National Renderers Association letter to Animal Protein Producers, 1989.

105. FDA, ''Report of Findings of Directed Inspections of Sheep Rendering Facilities,'' January 1993.

106. A joint statement by National Livestock and Professional Animal Health Organizations regarding a voluntary Ban on Ruminant Derived Protein in Ruminant Feed Recommendations, press release March 29, 1996.

107. USDA News Release No. 0159.96, ''USDA, U.S. Public Health Service Announce Additional Steps, Support for Industry Efforts to Keep U.S. Free of BSE,'' March 29, 1996.

108. Zimbleman, Robert G. (representing the American Society of Animal Science), April 8, 1996, letter to Gary Weber, National Cattleman's Beef Association.

109. Weber, G. M., National Cattlemen's Beef Association, Comment No. 280, June 13, 1996.

110. Anonymous, Comment No. 279, June 13, 1996.

111. Andrews, C. D., et al., ''Detection of Beef, Sheep, Deer, and Horse Meat in Cooked Meat Products by Enzyme-Linked Immunosorbent Assay,'' *Journal of Association of Analytical Chemist International,* 75:572–576, 1992.

112. Berger, R. G., et al., ''Detection of Poultry and Pork in Cooked and Canned Meat Foods by Enzyme-Linked Immunosorbent Assays,'' *Journal of Association of Analytical Chemist International,* 71:406–410, 1988.

113. Lamming, E., ''Bovine Spongiform Encephalopathy and Other Spongiform Encephalopathies,'' in ''The Report of the Expert Group on Animal Feedingstuffs to the Minister of Agriculture, Fisheries, and Food, the Secretary of State for Health and the Secretaries of State for Wales, Scotland, and Northern Ireland,'' 1992.

114. Eastern Research Group, ''Cost Analysis of Regulatory Options to Reduce the Risk of an Outbreak of Bovine Spongiform Encephalopathy (BSE),'' July 1996.

115. Ministries of Agriculture, Fisheries and Foods, ''Programme to eradicate BSE in the United Kingdom,'' May 1996.

116. Hoinville, L. J., ''Decline in the Incidence of BSE in Cattle Born After the Introduction of the 'Feed ban','' *Veterinary Record,* 134:274–275, 1994.

117. United Kingdom, Ministries of Agriculture, Fisheries and Foods, Animal Pharm, March 1994.

118. Mathews Jr., K.H., et al., Bovine Spongiform Encephalopathy: A Qualitative Economic Assessment, USDA Livestock Marketing Information Center, May 10, 1996.

119. USDA, Agricultural Statistics, 1996.

120. ''Swiss Plan Mass Cattle Slaughter,'' *Animal Pharm,* No. 357:p.6, Sept. 20, 1996.

121. United Kingdom, Ministries of Agriculture, Fisheries and Foods, *BSE: Government Measures to Assist the Beef industry,* Aug. 19, 1996.

122. Ashworth, S. W., and D. D. Mainland, ''The Economic Impact of BSE on the United Kingdom Beef Industry,'' *Outlook on Agriculture,* Vol. 24,3, pp. 151–154, 1995.

123. Duewer, L.A., USDA, Economic Research Service, personal communication, October 31, 1996; Putnam, Judith J., and J. E. Allshouse, *Food Consumption Prices and Expenditures, 1970–94,* USDA, Economic Research Service, Statistical Bulletin No. 928, Table 45, 1996.

124. Marsh, J. M., Derived Demand Elasticities: Marketing Margin Methods versus an Inverse Demand Model for Choice Beef, *Western Journal of Agricultural Economics,* vol.16 no.2, pp.382–391, 1991.

125. Lenard, Thomas M., Preliminary Economic Analysis of a Ruminant-to-Ruminant Feeding Ban, Prepared for American Feed Industry Association. Comments submitted to FDA Docket No. 96N–0135.

XIII. Request for Comments

Interested persons may, on or before February 18, 1997, submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 589

Animal feeds, Animal foods, Food additives.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 589 be amended as follows:

PART 589—SUBSTANCES PROHIBITED FROM USE IN ANIMAL FOOD OR FEED

1. The authority citation for 21 CFR part 589 continues to read as follows:

Authority: Secs. 201, 402, 409, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 342, 348, 371).

2. New § 589.2000 is added to subpart B to read as follows:

§ 589.2000 Animal proteins prohibited in ruminant feed.

(a) *Definitions.* (1) *Protein derived from ruminant and mink tissues* means any protein-containing portion of ruminant animals or mink, excluding blood from bovines, milk proteins and gelatin.

(2) *Renderer* means any firm or individual that processes slaughter byproducts, animals unfit for human consumption, meat scraps or food waste. The term includes persons who collect such materials and subject them to minimal processing, or distribute them to firms other than renderers whose intended use for the products may include animal feed. The term includes renderers that also blend animal protein products.

(3) *Blender* means any firm or individual which obtains processed animal protein from more than one source or from more than one species, and subsequently mixes (blends) or redistributes an animal protein product.

(4) *Feed manufacturer and distributor* includes manufacturers and distributors of complete and intermediate feeds intended for animals, and includes on-farm in addition to off-farm feed manufacturing and mixing operations.

(5) *Nonruminant protein* includes protein from nonruminant animals and from vegetable sources.

(b) *Food additive status.* The Food and Drug Administration has determined that protein derived from ruminant and mink tissues is not generally recognized as safe for use in ruminant feed because it may contain transmissible spongiform encephalopathy (TSE)-infective material, and is a food additive subject to section 409 of the Federal Food, Drug, and Cosmetic Act (the act). In the absence of a regulation providing for its safe use as a food additive under section 409 of the act, the use or intended use in ruminant feed of any material that contains protein derived from ruminant and mink tissues causes the feed to be adulterated and in violation of the act, unless it is the subject of an effective notice of claimed investigational exemption for a food additive under § 570.17 of this chapter. The Food and Drug Administration has determined that ruminant and mink derived protein is not prior sanctioned for use in ruminant feeds.

(c) *Requirements for renderers that are not included in paragraph (e) of this section.* (1) Renderers that manufacture products that contain or may contain protein derived from ruminant and mink tissues and that are intended for use in animal feed shall take the following measures to ensure that materials identified in paragraph (b) of this section are not used in the feed of ruminants:

(i) Label the materials as follows: ''Contains (or may contain) protein derived from ruminant and mink tissues. Do not feed to ruminant animals, and do not use to manufacture feed intended for ruminant animals''; and

(ii) Maintain copies of sales invoices for the materials, and make the copies available for inspection and copying by the Food and Drug Administration.

(2) Renderers described in paragraph (c)(1) of this section will be exempted from the requirements of paragraphs (c)(1)(i) and (c)(1)(ii) of this section if they:

(i) Use exclusively a manufacturing method that has been validated by the Food and Drug Administration to deactivate the agent that causes TSE's and whose design has been made available to the public; or

(ii) Use routinely a test method that has been validated by the Food and Drug Administration to detect the presence of the agent that causes TSE's and whose design has been made available to the public. Products found to contain the agent that causes TSE's shall be labeled ''Not for Use in Animal Feed.'' Records of the test results shall be made available for inspection by the Food and Drug Administration.

(3) Renderers described in paragraph (c)(1) of this section who are not exempted under paragraph (c)(2)(i) or paragraph (c)(2)(ii) of this section will be exempted from the requirements of paragraph (c)(1)(ii) of this section if they use a permanent method, approved by FDA, to mark the presence of the materials. If the marking is by the use of an agent that cannot be detected on visual inspection, the renderer must use an agent whose presence can be detected by a method that has been validated by the Food and Drug Administration and whose design has been made available to the public.

(d) *Requirements for protein blenders, and feed manufacturers and distributors, that are not included in paragraph (e) of this section.* (1) Protein blenders, and feed manufacturers and distributors, that manufacture, blend, process and distribute products that contain or may contain protein derived from ruminant and mink tissues shall:

(i) Comply with paragraph (c)(1) of this section, and

(ii) Maintain copies of invoices for purchase of animal protein products or feeds containing such products, and make copies available for inspection and copying by the Food and Drug Administration.

(2) Protein blenders, and feed manufacturers and distributors, shall be exempt from paragraphs (d)(1)(i) and (d)(1)(ii) of this section if they:

(i) Purchase animal protein products from renderers that certified compliance with paragraph (c)(2) of this section or purchase such materials from parties

that certify that the materials were purchased from renderers that certified compliance with paragraph (c)(2); or

(ii) Comply with the requirements of paragraph (c)(2) of this section where appropriate.

(3) Protein blenders, and feed manufacturers and distributors, shall be exempt from paragraph (c)(1)(ii) of this section if they:

(i) Purchase animal protein products that are marked or purchase such materials from renderers that certified compliance with paragraph (c)(3) of this section, or purchase such materials from parties that certify that the materials were purchased from renderers that certified compliance with paragraph (c)(3) of this section; or

(ii) Comply with the requirements of paragraph (c)(3) of this section where appropriate.

(4) Copies of certifications as described in paragraphs (d)(2) and (d)(3) of this section, shall be made available for inspection and copying by the Food and Drug Administration.

(e) *Requirements for persons that intend to separate ruminant/mink and nonruminant/mink materials.* (1) Renderers, protein blenders, feed manufacturers and distributors, haulers and others that manufacture, process, blend and distribute both protein products derived from ruminant and mink tissues or feeds containing such products, and protein products from other animal tissues or feeds containing such products, and that intend to keep those products separate shall:

(i) Comply with paragraphs (c)(1) or (d)(1) of this section as appropriate except that the labeling requirement shall apply only to products derived from ruminant and mink tissues or feeds containing such products;

(ii) In the case of a renderer, obtain nonruminant (excluding mink) materials only from single-species facilities;

(iii) Provide for measures to avoid commingling or cross-contamination:

(A) Maintain separate equipment or facilities for the manufacture, processing, or blending of such materials; or

(B) Use clean-out procedures or other means adequate to prevent carry-over of ruminant and mink derived protein into animal protein products or feeds that may be used for ruminants; and

(iv) Maintain written procedures specifying the clean-out procedures or other means, and specifying the procedures for separating ruminant and mink materials from nonruminant materials (excluding mink) from the time of receipt until the time of shipment.

(2) Renderers, blenders, and feed manufacturers and distributors will be exempted from appropriate requirements of paragraph (e)(1) of this section, if they meet the appropriate criteria for exemption under paragraphs (c)(2) or (c)(3), and (d)(2) or (d)(3) of this section.

(f) *Requirements for establishments and individuals that are responsible for feeding ruminant animals.* Establishments and individuals that are responsible for feeding ruminant animals shall maintain copies of purchase invoices and labeling for all feeds received, and make the copies available for inspection and copying by the Food and Drug Administration.

(g) *Adulteration and misbranding.* (1) Animal protein products, and feeds containing such products, that are not in compliance with paragraphs (c) through (f) of this section, excluding labeling requirements, will be deemed adulterated under section 402(a)(2)(C) or 402(a)(4) of the act.

(2) Animal protein products, and feeds containing such products, that are not in compliance with the labeling requirements of paragraphs (c) through (f) of this section will be deemed misbranded under section 403(a)(1) of the act.

(h) *Inspection; records retention.* (1) Records that are to be made available for inspection and copying, as required by this section, shall be kept for a minimum of 2 years.

(2) Written procedures required by this section shall be made available for inspection and copying by the Food and Drug Administration.

Dated: December 27, 1996.

David A. Kessler,

Commissioner of Food and Drugs.

Donna E. Shalala,

Secretary of Health and Human Services.

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